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SUBACUTE ENCEPHALITIS OF LATER ADULT LIFE. MAINLY AFFECTING THE LIMBIC AREAS

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IN the last few years a number of cases of both acute and subacute encephalitis have been reported which have not been easy to classify and in which a peculiar feature has tended to recur—that is, the inflammatory reaction has been most severe in the region of the temporal lobes (Greenfield, 1950; Krücke, 1957; Fields and Blattner, 1958; Aszkanazy, Tom and Zeldowicz, 1958; and others).

This topographical bias is striking and could scarcely have been overlooked in the earlier detailed studies of encephalitis. Its identification appears to reflect a new and material departure from the established patterns, and is of particular interest at a time when the temporal areas are the centre of so much attention, both clinical and pathological.

The present paper describes firstly the clinical and pathological findings in 3 adult cases of encephalitis in which the brunt of the inflammatory process involved the structures of the "limbic" lobes and secondly, discusses the relation of these cases to others of an apparently similar type which have been recently recorded.

Case I.—C. J. J., male aged 53. There was no personal or family history of nervous or mental abnormality and the physical health of the patient had always been good. He had worked for thirty years as a flour blender.

Six weeks before admission to the Maudsley Hospital, his wife noticed that he had become dazed and lethargic. A week before admission he suddenly became terrified, saying that he was "fighting for his life." After this brief episode he remained anxious and restless.

On admission on 18.9.56 he was profoundly depressed and agitated. He spoke slowly, continually reproaching himself, and he occasionally perseverated. He seemed perplexed and at times would laugh or prostrate himself on the ground for no apparent reason. Apart from a variable tremor of the outstretched hands there were no abnormal neurological signs and general examination was negative. The blood pressure was 180/80. No convincing evidence of an organic disorder was found and a provisional diagnosis of involutional depression was made.

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A course of electro-convulsive therapy was begun. After three treatments he became violent and abusive and was doubly incontinent, but he then steadily improved and he was discharged ten weeks after admission.

Laboratory investigations.—The Wassermann, Kahn, and Cardiolipine reactions in the blood were all negative, and an electroencephalogram carried out during this period was normal.

The patient returned to work, but although his wife thought he had recovered his employer subsequently reported that he had needed supervision. In February 1957 the patient began to have minor attacks each lasting a few minutes, consisting of nausea and an epigastric sensation together with sweating and alteration in colour. At times he complained of a curious smell associated with inability to speak.

In April 1957 he was investigated at St. Giles Hospital, Camberwell, on account of a sudden, brief loss of consciousness with convulsive movements. The only abnormal finding consisted of slightly brisker reflexes in the left lower limb. The cerebrospinal-fluid was examined and found to have a normal composition with a negative Wassermann reaction.

The minor attacks continued up to three times a day, his memory deteriorated and occasionally he complained of headaches.

An electro-encephalogram in August 1957 revealed sharp waves over both fronto-temporal areas. A further record with sphenoidal electrodes suggested that these arose from foci under both temporal lobes. The right side appeared to be the more abnormal.

In October 1957 he was readmitted to the Maudsley Hospital. He was apathetic, disorientated, and showed severe impairment of memory. He rarely spoke spontaneously but replied coherently to questions. Neurological examination revealed a coarse tremor of the outstretched hands and occasionally of the face.

No appreciable change occurred during the first month. Then he again complained of periodic headache, became drowsy and refused to eat. The lower limbs, particularly the left, were spastic, and the plantar responses at times were extensor.

He passed into coma and died five hours later, six and a half weeks after the second admission. He had been ill for fourteen months.

Post-mortem examination.—At autopsy, performed seven hours after death, there was no wasting or any external sign of disease. Apart from purulent bronchitis no other contributory cause of death was found. A small leiomyoma (histologically verified) was present in the left kidney. The skull, dura mater and the venous sinuses were normal. The brain was suspended intact in 10 per cent formalin.

Macroscopic appearances of the fixed brain.—The weight was 1,600 grammes. The leptomeninges and blood vessels were normal and there was no congestion or swelling.

In coronal slices, 1·0 cm. thick, abnormalities were confined to the hippocampi and the amygdaloid nuclei. There was a mottled appearance in the right pes hippocampus extending back into the Sommer sector of the hippocampus proper. Structural definition was blurred in the left hippocampus and in both amygdaloid nuclei.

The lateral ventricles were slightly dilated. The central white matter of the cerebral hemispheres appeared normal as did the cerebellum and brain-stem.

Microscopical examination.—Coronal blocks from both frontal, temporal, parietal and occipital lobes (including amygdaloid nuclei, basal ganglia, thalami and hypothalami) as well as from the mid-brain, pons, medulla, cerebellum and cervical spinal cord were embedded in celloidin. Sections were stained by the method of Nissl (using cresyl violet), of Heidenhain (for myelin), Holzer (for fibrous glia), Lendrum (for inclusion bodies), and with Mallory's phosphotungstic hæmatoxylin, hæmatoxylin and eosin and with iron hæmatoxylin and van Gieson's counter-stain.

Leptomeninges.—There was a slight increase in collagen and moderate cuffing of the smaller vessels (mainly veins) with lymphocytes and a few plasma cells. This perivascular infiltration was greatest in the floor of the collateral, inferior temporal, orbital, olfactory and anterior cingulate sulci. Slight patchy perivascular infiltration was occasionally seen both over the inferior half of the occipital lobe and in the dorsal and medial parts of the frontal lobes.

Clusters of inflammatory cells were also seen, usually around vessels, on the ventral aspect of the mid-brain, pons and medulla, and were sparsely scattered in the leptomeninges of the inferior cerebellar vermis.

Cortex, white matter and diencephalon.—The essential pathological process in the cortex was one of encephalitis with perivascular cuffing, neuronal destruction and glial nodule formation. The parenchyma was infiltrated with small numbers of lymphocytes, a few plasma cells and many glial elements, including astrocytes, rod cells and lipid phagocytes (fig. 1). There was a corresponding degree of inflammation of the related white matter. Hæmorrhage and tissue necrosis were not seen.

Inflammatory changes were most marked in the dorsal half of the amygdaloid nucleus and then in decreasing order of severity, in the hippocampus, hippocampal and fusiform gyri, the limen insulæ, and the ventral half of the claustrum. Only the anterior halves of the fusiform gyri were involved, the right more than the left. Inflammation of the white matter was most severe in the hippocampal and fusiform gyri, the right side being more affected than the left. A diffuse pallor of myelin staining was associated with subcortical perivascular cuffing most intense in the crowns of the gyri. There was considerable astrocytic proliferation with fibre formation greatest in the hippocampal gyrus. The process had died out at the posterior end of the hippocampal gyrus while anteriorly only the medial aspect of the temporal pole was involved in continuity with the linen insulæ. The extreme posterior end of the orbital surface of the frontal lobe showed evidence of inflammation, but the whole convexity and medial surface including the cingulate gyri were spared. In the temporal lobe the lateral limit of the process was the inferior temporal sulcus so that the superior, middle and inferior temporal gyri were unaffected. The precentral gyrus, the post-central gyrus and the reminder of the parietal as well as the occipital lobe, were similarly spared.

In the amygdaloid nucleus and the hippocampus inflammation was widespread. Within the latter it was most severe in the subiculum with numerous glial nodules, a dense astroglial and microglial reaction, and a patchy destruction of the pyramidal neurones (fig. 2). The superficial fibres of the subiculum showed partial demyelination but there was no appreciable demyelination of the alveus or fimbria. The process could be traced into the cortex of the hippocampal gyrus where it was less intense. On both sides the whole Ammon's horn apart from H2 showed marked loss of nerve cells as well as a dense fibrous gliosis, suggesting that the reaction had been present for some time. The dentate gyrus was interrupted by several gaps of total neuronal destruction largely around blood vessels. Vacuole formation was seen in damaged neurones both in the amygdaloid nucleus and, mainly, the subicular zone of pes hippocampus and hippocampus proper (fig. 3). Demyelination in the amygdaloid nucleus was marked on the left and almost complete on the right.

A careful search in sections of the inflamed regions stained with Lendrum's phloxine tartrazine and with hæmatoxylin and eosin failed to reveal any intra-nuclear or intracytoplasmic inclusion bodies.

The lingual gyrus and all the gyri of the occipital lobe showed no evidence of inflammation other than in the leptomeninges as already described. Similarly there were no abnormalities in the insular cortex of either side.

In the right optic tract at the level of the mammillary bodies there was a central oval

area of partial demyelination corresponding to a dense collection of astrocytes including binucleate and gemistocytic forms. This lesion did not extend more than a centimetre posteriorly and anteriorly had disappeared at the level of the chiasma.

The centrum ovale, corpus callosum, internal capsule and white matter of the brain stem and cerebellum were normal.

Thalamus.—A few cuffed vessels were present on the lower aspect of the anterior tubercle and along the inner aspect of the dorsomedial nuclei, more on the right than on the left. Adjacent neurones showed satellitosis.

Hypothalamus.—The mammillary bodies, paraventricular and supraoptic nuclei and the preoptic region showed slight perivascular cuffing, glial nodule formation and neuronal damage. A fine fibrous gliosis was present.

Lentiform and caudate nuclei.—In the putamina a few moderately cuffed vessels were seen in the ventrolateral parts and along the external medullary laminæ. Similarly in the caudate nuclei, the sole change was perivascular cuffing round the thalamostriate vein and an occasional vessel in the nuclear substance.

One or two cuffed vessels were seen at the lower border of the globus pallidus.

Subthalamic region.—The subthalamic nuclei, Forel's fields, zona incerta and red nuclei were normal.

Brain-stem and cerebellum.—A few lymphocytes were seen in the perivascular spaces of the substantia nigra; the pigmented cells were intact. Very slight perivascular cuffing was seen round a vessel in the pigmented nucleus of the pons and one or two in the tegmental region. The basilar portion was normal. Apart from a single cuffed vessel in the area postrema, no abnormalities were seen in the medulla.

The cervical spinal cord was normal.

There was considerable venous congestion and an occasional cuffed vessel in the white matter of the folia of the inferior cerebellar vermis. The dentate nuclei appeared normal as did the Purkinje and granule cells and the Bergmann glia.

In Bielschowsky preparations there was no evidence of Alzheimer's neurofibril change in the neurones of the cerebral cortex, amygdaloid nuclei, Ammon's horns, or in the substantia nigra.

Case 2.—A. S. D., male aged 58. One daughter suffered from schizophrenia but there was no other family or previous personal history of mental or nervous disorder. Following gas poisoning in the First World War he had been subject to bouts of bronchitis and pneumonia. In 1918 he had a gonorrhœal infection and possibly a second fifteen years later.

The patient was admitted to Warley Hospital, Brentwood, on 6.4.56 with a history of a respiratory infection a month earlier followed by severe depression with weeping and feelings of unworthiness. He had threatened to end his life and he became intensely religious; he was easily excited. He complained of headaches and at times was unsteady on his feet.

On admission he was correctly orientated and rational but was anxious, agitated and suspicious. Speech was slightly slurred, but neurological examination was completely negative. Blood pressure was 125/80. For the first few days he was emotionally labile, restless and anxious, at times being over-talkative and expressing grandiose delusions. General paralysis of the insane was tentatively diagnosed. A few days after admission the cerebrospinal fluid was found to contain 24 cells/cu.mm. (97 per cent lymphocytes), protein 90 mg./100 ml. and the Lange colloidal gold curve was 5555554321. The Wassermann reaction in the blood and cerebrospinal fluid was negative, however (as were the Price's Precipitation Reaction, and a Kahn test). These

findings were confirmed by the Venereal Disease Reference Laboratory of the London Hospital where a Treponemal immobilization test was also carried out with a negative result. A syphilitic infection was therefore completely excluded.

The patient's mental state deteriorated, he appeared hallucinated, was degraded in his habits, and incontinent. Speech was slurred, rambling and incomprehensible. His gait became extremely unsteady and in falling he fractured a humerus and two metacarpal bones.

In the early weeks in hospital there was an occasional evening temperature up to 99·6° F.; this then settled for several weeks but again started to fluctuate up to 101° in the days before death. Re-examination of the cerebrospinal fluid three weeks after admission showed 146 white cells (99 per cent lymphocytes), protein content of 100 mg./100 ml., and the Lange colloidal gold curve was 5555555432. On May 8, he collapsed during the night and was unrousable. After ten hours, however, he gradually recovered. During the last week of his life his condition appeared to have slightly improved, but on May 24 another episode of coma occurred and he died an hour later, about eleven weeks after the onset of the illness.

Post-mortem examination.—This was carried out thirty-six hours after death by Dr. K. A. D. Turk to whom we are most grateful for this summary of his findings.

Death was attributed to chronic bronchitis and bronchopneumonia in the presence of a subacute encephalitis. The body was that of a poorly nourished man with recent loss of weight.

Lungs.—Fibrous adhesions over right upper lobe. Bilateral chronic bronchitis and emphysema, with œdema and early bronchopneumonic consolidation of the lower lobes. Several mediastinal and hilar lymph nodes were enlarged and consisted of soft white tissue but no primary growth was found in the lungs (or elsewhere in the body). Histological examination showed the nodes to be extensively replaced by oat-shaped cells, appearing identical to those seen in anaplastic bronchial carcinoma. Other organs, apart from the brain, showed only changes due to venous congestion.

Macroscopic appearances of the brain.—A thin layer of altered blood was present over the left hemisphere and the brain appeared moderately congested. No meningeal exudate or thickening, vascular disease or other localized lesion was found. The cut brain, fixed in 10 per cent formalin, weighed 1,255 grammes. It was slightly swollen; no atrophy or ventricular dilatation were evident. The contrast between the cortex and white matter at the temporal poles was poor and the tissue had an unusual soft creamy appearance. The brain in other respects appeared normal. The spinal cord was not examined.

Macroscopical examination.—Blocks and staining methods were essentially similar to those of Case 1.

Evidence of encephalitis was scattered throughout the brain to some slight extent but it was strikingly intense in the region of the temporal lobes and the striatum. Slight changes were found in the brain-stem and cerebellum.

In the severely affected areas massive perivascular infiltration by lymphocytes and plasma cells was accompanied by the degeneration and the loss of many nerve cells with an intense glial reaction, both astrocytic and microglial.

The changes mainly involved grey matter but when they were marked the adjacent white matter was also materially damaged (fig. 4). The distribution of the changes is described in greater detail.

Meninges.—The leptomeninges over the brain as a whole showed no fibrous thickening. Diffuse infiltration with lymphocytes and occasional areas of intense perivascular cuffing were present, usually when the underlying cortex was also heavily involved. In some areas—occipital, parietal, and central—the meninges were more affected than the underlying cortex.

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Cortex and subadjacent white matter.—The intensity of the inflammatory reaction was greatest in the insula and infero-medial region of the temporal lobes. At the level of the uncus, the destruction was most marked and both the amygdaloid nucleus and the white matter deep to it were markedly affected (fig. 5); in the latter a noticeable feature was the proliferation of many large pale swollen astrocytes amid the demyelination. Cortical devastation was also present in the hippocampal gyrus (fig. 6), the insula (particularly its ventral part), and to a lesser extent the first temporal gyrus, but there was a distinct tendency for the ventrolateral part of the temporal lobes to be less involved (figs. 7–9). More posteriorly, the brunt of the changes was found in the hippocampal gyrus, the subiculum, and the Ammon's horn.

At the level of the head of the caudate nucleus and more anteriorly through the prefrontal areas, the orbital and the cingular gyri were severely affected, the convexity showing only slight patchy evidence of encephalitis. The central region, the parietal convexity and the occipital lobes were largely spared.

Corpus striatum.—The inflammatory reaction was severer in the striatum than in any other subcortical grey matter. In the caudate nucleus, putamen and ventral half of the claustrum, intense perivascular infiltration was widespread, and degeneration and loss of nerve cells was marked.

Diencephalon.—In the thalamus, subthalamus, and the hypothalamus, there was mild cuffing of an occasional vessel with little glial reaction. A few loosely packed glial nodules were present in the thalamus.

Brain-stem.—In the mid-brain, the tectum, tegmentum and peduncles were intact. In the substantia nigra, a very few vessels showed slight cuffing; the pigmented nerve cells were not appreciably damaged and there was no gliosis. In the dorsal part of the pons an occasional glial nodule was present and slight perivascular cuffing was seen in the pontine nuclei. The inferior olives in the medulla were severely damaged (fig. 10), the vessel walls being heavily infiltrated. Both inferior olives showed widespread patchy loss of nerve cells with much microglial and astrocytic proliferation, and a dense glial fibrosis. Elsewhere in the medulla a few loosely packed groups of glial cells were seen and an occasional vessel showed slight cuffing.

Cerebellum.—There was slight patchy lymphocytic infiltration of the leptomeninges. There was considerable loss of Purkinje cells and a marked astrocytic and microglial reaction was present. The granular cells were unaffected but there was an increase in glial cells and also occasional cuffing of the vessels in the white matter. The dentate nuclei had undergone a patchy loss of nerve cells with a glial reaction similar to, but much less severe than, that in the inferior olives.

Special staining methods did not show any excess of iron, nor were spirochætes or inclusion bodies identified. Alzheimer's neurofibrillary changes were not seen.

Case 3.—W. W., male aged 56. Previous health had been excellent apart from winter bronchitis.

He was admitted to Dulwich Hospital on 25.11.54, six weeks after the onset of aching pain across the shoulders and later down the arms. This had improved by the time of admission, but he complained of pins and needles in the hands and also of tiredness and depression. His general condition was good. The blood pressure was 160/100.

The evening temperature rose at times to 100° F. Soon after admission the white cell count was 2,600 c.mm. (55 per cent polymorphs, 41 per cent lymphocytes, 2 per cent eosinophils, and 2 per cent monocytes). In view of the pyrexia and low white cell count with relative lymphocytosis, serum agglutination reactions were carried out by the Virus Reference Laboratory, Colindale. All these were negative, apart from

that for psittacosis, which was positive at 1/20, the titre remaining unchanged on two further examinations at monthly intervals. The result suggested that a psittacosis-like infection had occurred in the remote past. Ten days after admission the cerebrospinal fluid contained 37 lymphocytes/c.mm. and 90 mg./100 ml. of protein. The Wassermann reaction was negative and the Lange colloidal gold curve was normal.

Three weeks later his wife noted a change in his personality, in that he showed no concern about his illness or the financial difficulties of the family. He was apathetic, disorientated, and his memory was impaired. The knee and ankle jerks were difficult to elicit.

A further examination of the cerebrospinal fluid showed the presence of 22 lymphocytes, 6 polymorphs, and 33 red cells per c.mm. The protein content was 70 mg./100 ml. (with detectable globulin) and sugar 70 mg./100 ml. An X-ray of the chest revealed a small rounded shadow in the lower part of the right hilum, and this was interpreted as possibly due to a bronchial carcinoma. Although bronchoscopy was negative, further X-rays showed a slight increase in the size of the shadow. This finding, coupled with the mental deterioration, led to a diagnosis of cerebral secondary deposits.

He returned home at the end of January 1955, but was readmitted early the following month, disorientated, with a tendency to confabulate, and complaining of occasional headaches. The knee-jerks were absent, the ankle-jerks feeble, and the plantar responses extensor. The cerebrospinal fluid contained 12 lymphocytes/cmm. and 30 mg. protein/100 ml. again with detectable globulin. Another X-ray of the chest showed a slight increase in size of the hilar shadow. The electroencephalogram was very abnormal with diffuse slow activity at 0·75 to 3·0 cycles per second and only alpha potentials in the post-central areas but without significant asymmetry. During the last week of life there were occasional periods of coma, and he died on 7.5.55, seven months after the onset of the illness.

Post-mortem examination.—This was carried out six hours after death by Dr. B. S. Cardell, for whose co-operation we are grateful.

Widespread bronchopneumonia was present. An encapsulated mass at the root of the right lung was found on histological study to consist of fibrotic lymph nodes. Naked-eye and histological examination of other tissues apart from the brain showed no abnormalities.

Macroscopic appearances of the brain.—The fresh brain weighed 1,450 grammes. On coronal section the medial convolutions of the temporal lobe appeared swollen and discoloured to the naked eye.

Microscopical examination revealed some degree of inflammatory change throughout the cerebral hemispheres, but this was most severe in the medial parts of the temporal lobes.

Distribution of changes.—In the frontal and occipital lobes and around the central fissures the changes were as follows:

The leptomeninges were considerably thickened and diffusely infiltrated with lymphocytes. Both in the cortex and in the white matter slight cuffing was present around a few vessels and there was mild proliferation of astrocytes and microglia. No loss of myelin was seen.

In the orbital cortex of the frontal lobes, in the insula, the claustrum, and in the inferior temporal convolutions, the inflammatory changes were moderately severe. In the adjacent white matter, particularly in the temporal lobes, considerable perivascular and neuroglial reaction as well as a diffuse loss of myelin had occurred.

The claustrum showed a moderately severe inflammatory reaction with some loss of

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nerve cells and marked astrocytic proliferation. There was considerable cuffing round the vessels in the striatum, and in the medial border of the thalamus and the hypothalamus. The rest of the thalamus and the pallidum showed only a slight inflammatory reaction.

The white matter of the internal capsule, basal ganglia and optic chiasma showed slight inflammatory reaction by no demyelination.

The histological changes were most severe in the hippocampal gyrus,the hippocampus and the amygdaloid nucleus (fig. 11). The architectonic pattern had been completely broken up by the intense inflammatory reaction and many nerve cells had disappeared. The white matter adjacent to the amygdaloid nucleus showed considerable inflammatory change and demyelination but in the hippocampal gyrus such changes were less severe.

In the mid-brain there was evidence of inflammation in the substantia nigra with cuffed vessels, destruction of pigmented nerve cells and melanin pigment lying free in the tissue or within phagocytes. There were a few glial nodules in the oculomotor nuclei and in the tectum.

Scattered small glial nodules were seen in the basilar part of the pons and occasional slight round cell infiltration of meninges and perivascular spaces was present in both pons and midbrain.

The spinal cord and medulla were not examined.

No inclusion bodies were detected in any glial cells or in the neurones.

Discussion

Although these 3 cases were diagnostic problems during life the possibility of a viral encephalitis had been seriously considered in 2 (Cases 2 and 3), and in the latter extensive but negative agglutination reactions had been carried out. In none was any attempt made to identify a virus after death.

In Cases 2 and 3 an evening temperature up to 100° F. had occurred initially at times; in the latter it had subsided after the first few weeks.

The clinical histories showed no close similarity when studied in retrospect. The first case presented as a severe depression coloured by a certain bizarreness of behaviour. Later minor attacks of a "temporal lobe" type developed and on one occasion generalized convulsive movements occurred.

In the second case the patient became severely depressed following a respiratory infection (to which he had been prone for many years). At one time the possibility of G.P.I. was considered, partly in view of the clinical picture and partly because of the abnormal cerebrospinal fluid with a colloidal gold curve of 5555554321. No serological evidence of syphilis however was found either in the blood or in the cerebrospinal fluid, and a Treponemal immobilization test was also negative. A paretic colloidal gold curve moreover is a common finding in cases of subacute encephalitis.

In the third case the illness began with pains in the shoulders and arms which after several weeks were complicated by feelings of tiredness and depression.

A progressive dementia ending in one or several brief periods of coma was common to all 3 cases.

None of these cases showed the myoclonic contractions, torsion spasms, or athetoid movements which are so characteristic of the Dawson-van Bogaert type of subacute encephalitis. Epileptic attacks occurred only in the first case and these were mainly "temporal lobe" in type.

In Case 3 a lung cancer had been suspected but was not confirmed *post mortem*. On the other hand in Case 2 several mediastinal lymph nodes were found after death to be partly replaced by malignant tissue histologically comparable to that seen in bronchial carcinoma. No primary growth was found, however, and no other secondary deposits were identified elsewhere in the body. It seems most unlikely that this finding is in any way related to the encephalitis but its occurrence should be noted.

Neuropathological findings.—The term "limbic lobe" is taken here to include the uncus and the amygdaloid nucleus, the hippocampus and dentate gyrus, the limen insulæ and the hippocampal and cingulate gyri.

Involvement of these regions was the salient topographical feature in each case, both from the macroscopic and the histological points of view. This observation does not imply any overstrict localization nor is it meant to suggest that the findings were always neatly confined to the limbic lobes. In Case 1, for example, the cingulate gyrus was not appreciably affected while in Cases 2 and 3 the striatum, insula, and to a lesser extent the superior and middle temporal gyri were demonstrably involved. Moreover occasional patches of mild inflammation were also seen in other parts of the cortex and in the thalamus, hypothalamus and in Case 2 in the lower brain-stem.

The histological appearances were those of a subacute encephalitis without hæmorrhage or necrosis. The changes were essentially confined to the grey matter, whether cortical or subcortical, and they only spread to contiguous white matter in the most severely affected areas. No intranuclear or intracytoplasmic inclusion bodies were demonstrated.

In view of these findings, and since the limited attempts to identify a causal agent had failed, the diagnosis of viral encephalitis must be inferred from the histological picture. Not only does the process appear typical of this but its limbic distribution is remarkably similar to that described in recent reports dealing with certain other examples of acute and subacute encephalitis (Krücke; Fields and Blattner; Aszkanazy, Tom and Zeldowicz). The two histological points that have been most emphasized in each attempt to classify such cases are, firstly, the demonstration of intranuclear inclusion bodies and, secondly, the distribution of the lesions. A third consideration is that of the acuteness of the illness.

The commonest form of acute encephalitis mainly to affect the temporal lobes is that related to herpetic infection—*acute encephalitis with nuclear*

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inclusions. According to the recent comprehensive review by Haymaker and his associates (Fields and Blattner) this is a disease of adults as well as infants, and in most cases lasts under three weeks. Histologically, type A intranuclear inclusion bodies are found in virtually every case coupled with the "striking and constant feature of necrosis of the temporal cortex accompanied by tissue breakdown . . . As to the topography of cerebral cortical involvement the temporal and the insular cortex was consistently affected. The same was true for the hippocampal formation which was practically always severely damaged. The gyrus cinguli also shared conspicuously in the necrosis, and in a few cases, the adjoining superior (mesial) frontal gyrus and the corpus callosum as well. In 9 cases (out of 37) there were lesions in frontal, parietal and/or occipital cortex, and in most of them the cortical lesions were most pronounced in regions adjoining the temporal lobe" (p. 154).

Cases of acute encephalitis mainly affecting the temporal lobes but without demonstrable inclusion bodies have also been recorded. Greenfield (1950) first reported these findings in a woman of 20 dying after an illness of three weeks. In the brain there was "hæmorrhagic congestion resembling infarction" in the right hippocampal gyrus and intense congestion of the medial surface of the right frontal pole and insula. No inclusion bodies were identified. In 1957 Crawford and Robinson reported 5 cases of necrotizing encephalitis in none of which were inclusion bodies identified. The distribution of the inflammatory reaction was not dealt with in detail, but in two of the three adult cases (Cases 2 and 3) the temporal lobes appear to have been predominantly affected. In 1958 Aszkanazy, Tom and Zeldowicz described the findings in 7 sporadic cases of encephalitis which had occurred in Canada in subjects between the ages of 17 and 53 years. 6 had survived less than three weeks (the seventh lived five months although the onset was fulminating) and in all "the noteworthy peculiarity was the massive necrosis of the temporal lobes and the adjacent regions" which semed "too constant to be fortuituous." In none, however, were inclusion bodies identified.

It is clear therefore that acute forms of encephalitis in adults exist which mainly involve the temporal lobes. In most, intranuclear inclusion bodies have been demonstrated; in a few they have not, and it is to these that the present cases would at first sight appear to be most closely related. Such a conclusion, however, would not be entirely correct, for in none of them could the course of the illness be described as acute. Pathologically, moreover, the findings were not those of recent hæmorrhage, necrosis, or frank tissue breakdown, but, while admittedly severe, were much more those of a well-established reaction. In other words, the cases are subacute.

Subacute encephalitis mainly involving the temporal lobes appears only to have been described as a feature of some cases belonging to the Dawson-

van Bogaert series (Krücke; Fields and Blattner). Originally reported as distinct conditions, these two—the subacute inclusion encephalitis of Dawson and the subacute sclerosing leuco-encephalitis of van Bogaert—are now generally considered to form a single clinico-pathological entity (Greenfield). On the clinical side, the age of onset has been almost exclusively below 21 (although two examples occurring at about 36 have been recorded) and some form of marked involuntary motor activity has usually been a major feature. Pathologically, a wide spectrum of change involving grey or white matter throughout the hemispheres is admissible, and inclusion bodies may or not be present. (It may be emphasized here that the absence of inclusion bodies can never be proved for there must always remain the possibility, and occasionally in the past there has been the fact, that at the time of the original report they were present but not seen.)

With this information in mind, it is difficult to accept the present cases, each occurring in the sixth decade, simply as belonging to the Dawson-van Bogaert type, which is overwhelmingly a disease of minors, and in which there would appear to be no more than an inconstant tendency for the pathological changes to concentrate in the region of the temporal lobes.

Too little is known, however, either about the ætiology of these newer encephalitides or about the meaning of their peculiar cerebral topography to justify any further discussion of their nosological position. In any case, this is more likely in the long run to be established by virus studies than by any assessment of the histological findings.

In these circumstances the present cases can only be described as examples of subacute progressive encephalitis occurring in later adult life and mainly affecting the limbic lobes. It cannot be asserted that they necessarily consitute a distinct form of viral encephalitis as their precise ætiology is unknown. Further, at the present time there are so few examples of subacute adult encephalitis of any other distribution that the separate delineation of these 3 cases seems justified.

Summary

The clinical and pathological findings are described in 3 cases of subacute encephalitis. The subjects were men between the ages of 53 and 58 and they were ill for three, seven and fourteen months respectively.

In each case evidence of a severe encephalitis was concentrated to a noticeable degree in the limbic areas of the brain. No inclusion bodies were identified.

The possible relation of these cases to other recent reports, both of acute and subacute encephalitis, is briefly discussed.

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LEGENDS TO FIGURES IN PLATES

PLATE XLIX

FIG. 1 (*Case* 1).—Subiculum showing round cell cuffing of a vessel, neuronal damage and proliferation of astrocytes and microglia. (Cresyl violet × 150.)

FIG. 2 (*Case* 1).—Hippocampus showing diffuse inflammation with neuronal destruction, capillary proliferation and diffuse gliosis. (Cresyl violet × 20.)

FIG. 3 (*Case* 1).—Amygdaloid nucleus. There is neuronal damage with vacuole formation perivascular cuffing and diffuse infiltration with astrocytes and rod cells. (Cresyl violet × 273.)

FIG. 4 (*Case* 2).—Myelin stained section of left temporal lobe and basal ganglia. There is partial loss of myelin around the lateral border of the amygdaloid nucleus (× 1·5). The numbers 1–5 mark the fields in each of the following 5 illustrations.

FIG. 5 (*Case* 2).—Field 1: Part of the amygdaloid nucleus and hippocampal gyrus to show the inflammatory reaction at its most severe. (Cresyl violet × 13.)

PLATE L

FIGS. 6–9 (*Case* 2).—Fields 2–5: These fields from medial to lateral show progressively less evidence of inflammation. (Cresyl violet × 13.)

FIG. 10 (*Case* 2).—Left inferior olive showing patchy loss of nerve cells, an acute gliosis and some cuffing of the adjacent vessels. (Cresyl violet × 13.)

FIG. 11 (*Case* 3).—Hippocampal gyrus and amygdaloid nucleus showing both the severe inflammatory reaction and disorganization of the normal architecture. (Cresyl violet × 10.)

PLATE XLIX

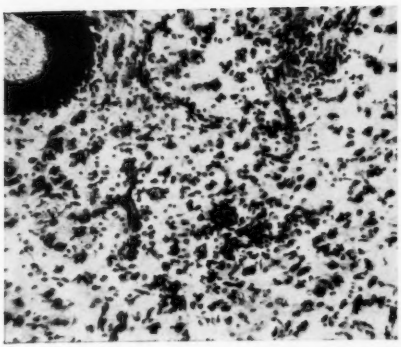

FIG. 1.

FIG. 2.

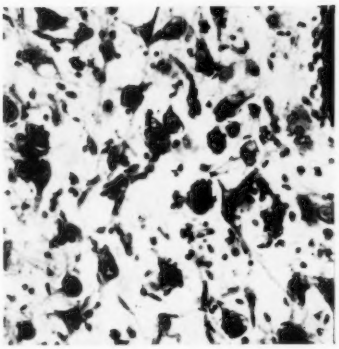

FIG. 3.

FIG. 4.

FIG. 5.

To illustrate article by J. B. Brierley, J. A. N. Corsellis, R. Hierons and S. Nevin.

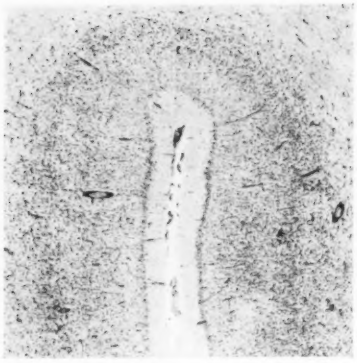

FIG. 6.—Field 2.

FIG. 7.—Field 3.

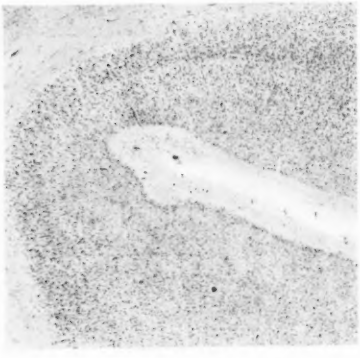

FIG. 8.—Field 4.

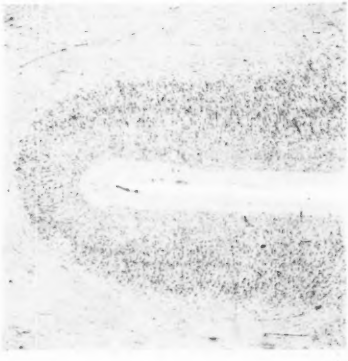

FIG. 9.—Field 5.

FIG. 10.

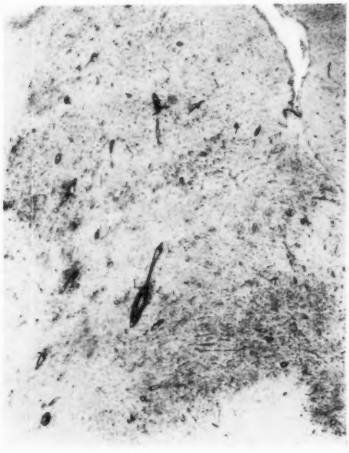

FIG. 11.

To illustrate article by J. B. Brierley, J. A. N. Corsellis, R. Hierons and S. Nevin.

METACHROMATIC LEUCO-ENCEPHALOPATHY: A FORM OF LIPIDOSIS

BY

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INTRODUCTION

THE delineation by Brain and Greenfield (1950) of a late infantile form of metachromatic leuco-encephalopathy has been followed by the important discovery that the brain in this condition contains a large increase in sulphatide (Jatzkewitz, 1958; Austin, 1959). Our study of two familial cases of this disorder has confirmed this finding and has led us to the conclusion that the relationship of metachromatic leuco-encephalopathy to the lipidoses is much closer than has hitherto been realized. The storage of metachromatic lipid in the nerve cells of the nuclei of the brain-stem was much more widespread than has been reported in previous cases and in several other ways there were close resemblances to the pathological features displayed by recognized diseases of lipid metabolism. Austin's conception of metachromatic leuco-encephalopathy as a "sulphatide lipidosis" seems to be fully substantiated.

CASE REPORTS

Case 1.—L. C., male. Born 15.9.52; died 22.8.55.

This boy was the third child in the family, the elder twins having died soon after birth. He was born at full term, his weight being 8 lb. 14 oz. There was some asphyxia at birth from which the child made a rapid and complete recovery. Development during the first year of life was normal. Walking, however, was delayed until the age of 19 months and he never walked well. His gait was stiff and clumsy, he tended to veer to the right and to fall frequently. In October 1954 he had a screaming attack during which he stared vaguely but had no convulsions. He had two more similar attacks during the following night. During the subsequent few days he was feverish and vomited several times. When he recovered from this illness his parents found that his gait had deteriorated and that he could not walk more than a few steps without support.

In December 1954 he was admitted to the Radcliffe Infirmary, Oxford. He was found to have a large head with a circumference of 20½ in. There was a fine nystagmus while looking to the left. There was some motor weakness and slight spasticity of both legs with brisk tendon-jerks and extensor plantar responses. He appeared to be intelligent and talked well for his age. A lumbar puncture yielded fluid under

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raised pressure which contained 105 mg. per cent protein and 3 lymphocytes per c.mm. He was thought to have a cerebellar tumour and was transferred to the Neurosurgical Unit where an air encephalogram was performed. This revealed slight dilatation of the lateral and third ventricles, but the fourth ventricle and cisterna magna were normal.

The subsequent history was one of gradual decline. He became more ataxic both in his upper and lower limbs and the nystagmus became more prominent. The weakness and spasticity of his lower limbs increased and he lost the power of walking, standing and ultimately sitting. He became dull and apathetic and gradually lost his speech although his vision and hearing remained apparently unimpaired. During the last three weeks of his life he became gradually weaker and succumbed to a respiratory infection at the age of 2 years 11 months.

Case 2.—M. C., female. Born 14.6.55; died 17.3.58.

This girl was the fifth child in the same family as in Case 1, the fourth child, also a girl, being alive and well. Birth was normal, at full term and the birth weight 8 lb. 4 oz. Early development was normal. She sat up at 8–9 months, crawled at 12 months and started talking single words at 11 months. In July 1956 she had a mild attack of measles. Since then she had periodic screaming attacks at night. She became easily tired and irritable and was disinclined to walk. In April 1957 she stopped feeding herself. At the same time her legs were noticed to be stiff.

On admission to the Radcliffe Infirmary in June 1957 she was drowsy and irritable, but appeared to see and hear. Her legs were extended and her neck retracted. The legs were spastic with brisk knee-jerks and extensor plantar responses. The cerebrospinal fluid contained 160 mg. per cent of protein and 4 lymphocytes per c.mm. An air encephalogram revealed slight dilatation of all four ventricles and free circulation of air into the basal cisterns and over the surface of the hemispheres.

On readmission in November 1957 her condition had deteriorated considerably. She did not laugh or smile, recognize objects or take any interest in her surroundings. She had developed difficulty in swallowing and was losing weight rapidly. Muscle tone in all limbs was now reduced and tendon reflexes were sluggish. The plantar responses were extensor. When disturbed the child became opisthotonic and held her breath until deeply cyanosed. During the final stage of the disease she developed flexion contractures of her lower limbs. She died of bronchopneumonia at the age of 2 years 9 months.

Examination of the Nervous System

Macroscopic Appearances

Case 1.—The brain weighed 1,334 grammes before fixation. In spite of its large size it was not tense, showed no flattening of the convolutions or evidence of incisural herniation. It was firm and tended to keep its shape after removal. The convolutional pattern was normal. On sectioning the brain after fixation the cerebral cortex appeared normal in thickness and consistency, but slightly more grey than usual. The white matter, on the other hand, was a dull, chalky white with some ill-defined greyish mottling in the central parts of the centrum ovale. The demarcation from the cortex was singularly sharp. The white matter of the hemispheres was soft and resilient in consistency, somewhat suggesting soft rubber. The lateral ventricles were slightly dilated. The claustrum was represented by a thin, linear slit separating the external capsule from

the white matter of the insula. The brain-stem and cerebellum appeared normal. The spinal cord was firm and of unusually large diameter, particularly in the cervical part. The meninges and blood vessels were normal.

Case 2.—The brain weighed 1,050 grammes before fixation and apart from its smaller size closely resembled that of the elder sibling. The only difference appeared in the cerebellum which was smaller and firmer and showed some shrinkage of the folia.

Histology

Frozen sections from representative areas in both brains were stained by standard methods for nerve cells, myelin, neuroglial fibres and fat. All sections were also stained either with toluidin blue or by the cresyl-violet-acetic acid method of Hirsch and Peiffer (1955). Special histochemical procedures and solubility tests were also carried out. In the first case large celloidin survey sections were also prepared and stained for nerve cells, axis cylinders and myelin. With certain exceptions to be noted later the histological appearances of the two cases were closely similar and to avoid repetition will be described together so as to give a composite picture.

Changes in the nerve cells.—The nerve cells of the cerebral cortex were normal as regards number and arrangement and did not contain metachromatic material. The thalamus showed an almost complete loss of nerve cells except for the centromedian nucleus and mid-line groups which appeared normal. The cells of the putamen and caudate nucleus were unaffected. In each claustrum the clefts already mentioned proved on microscopic examination to have ragged margins with no sign of a lining layer of neuroglia or connective tissue. There was no apparent loss of nerve cells adjacent to the cavities nor was metachromatic material found in the neurons of the preserved parts of the nuclei. The walls of a few vessels in the vicinity of the cavities contained droplets of neutral fat. The anterior and posterior parts of the claustrum, where there was no cavitation, showed an overgrowth of fibrous neuroglia which was almost as great as in the neighbouring white matter. Here and there the nerve cells appeared to be reduced in number and in many the cytoplasm stained feebly in Nissl preparations but there was no widespread destruction of cells in the areas of gliosis. Severe nerve-cell loss with metachromasia of the survivors was present in the globus pallidus and subthalamic nucleus. The external geniculate body showed similar appearances. The hypothalamic nuclei were normal except for the lateral nucleus of the mammillary body which was selectively involved by the storage of metachromatic lipid. The nuclei of the brain-stem were studied in detail, using the Hirsch-Peiffer stain for the demonstration of metachromatic inclusions (fig. 1, Plate LI). The results are shown in

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TABLE I.—DISTRIBUTION OF NEURONAL STORAGE IN THE NUCLEI OF THE BRAIN-STEM (THE FIGURES IN BRACKETS INDICATE CASE IN WHICH THE APPROPRIATE LEVEL WAS EXAMINED)

Severely affected		*Partially affected*		*Unaffected*	
Griseum pontis	(1, 2)	Colliculus superior	(1)	Area postrema	(1, 2)
N. ambiguus	(1, 2)	N. gigantocellularis	(1, 2)	Griseum centrale	(1)
N. arcuatus	(1, 2)	N. nervi trigemini sensibilis principalis	(2)	Locus cœruleus	(1)
N. cochlearis ventralis	(2)	N. olivaris inferior	(1, 2)	N. cochlearis dorsalis	(2)
N. conterminalis	(1, 2)	N. paragigantocellularis	(1, 2)	N. cuneatus medialis	(1)
N. corporis pontobulbaris	(1, 2)	N. pontis centralis	(2)	N. dorsalis vagi	(1, 2)
N. cuneatus lateralis	(1, 2)	N. præpositus hypoglossi	(1, 2)	N. Edinger Westphal	(1)
N. interstitialis	(1)	N. tractus spinalis trigemini	(1, 2)	N. gracilis	(1)
N. medullæ obl. lateralis	(1)	N. trapezoidalis	(2)	N. intercalatus	(2)
N. nervi abducentis	(2)	N. vestibularis medialis	(1, 2)	N. intercollicularis	(1)
N. nervi facialis	(2)			N. interpeduncularis	(1)
N. nervi hypoglossi	(1, 2)			N. olivaris superior	(2)
N. nervi trigemini mesenceph.	(1, 2)			N. raphæ obscurus	(2)
N. nervi trigemini motorius	(2)			N. raphæ pallidus	(2)
N. nervi trochlearis	(1)			N. ruber	(1)
N. oculomotorius principalis	(1)			N. substantiæ nigræ compactus	(1, 2)
N. paramedianus dorsalis	(2)			N. supratrochlearis	(1)
N. substantiæ nigræ reticulatus	(1, 2)			N. tractus solitarii	(1, 2)
N. vestibularis lateralis	(2)				
N. vestibularis spinalis	(2)				
N. vestibularis superior	(2)				

Table I, the nomenclature being that of Olszewski and Baxter's atlas (1954). In the spinal cord intracellular storage was conspicuous in the anterior horn cells and in the cells of Clarke's column. A posterior root ganglion (Case 1) showed large accumulations of metachromatic lipid in the nerve cells and small flecks in the capsule cells (fig. 2).

The cerebellar cortex was the only region showing substantial differences in the 2 cases. In the first case no abnormality was detected but in the second there was a diffuse loss of granule cells which was associated with the presence of large fibrous astrocytes (fig. 3). The great majority of Purkinje cells were preserved and showed no metachromatic lipid either in their cell bodies or dendrites. There were unusually large numbers of swellings ("torpedoes") on the axons of the Purkinje cells (fig. 4). Tangential and basket fibres were preserved. The molecular layer showed a well developed fibrous gliosis of the Bergmann astrocytes. The nerve cells of the dentate nuclei in both cases showed abundant lipid storage.

Changes in the white matter.—Myelination of the cerebral cortex was poor, there being few tangential fibres and scanty radial fibres, the majority of which were thin and beaded. Microglial cells containing flecks of metachromatic material were occasionally seen in the deeper cortical layers. Almost complete destruction of myelin sheaths and axis cylinders had occurred in the central part of the hemispheric white matter, the cores of the gyri and the arcuate fibres being better preserved, though not unscathed, as were also the alveus and fimbria. Yet both in frozen and celloidin sections stained for myelin the impression often given to the naked eye was that of only moderate demyelination on account of the presence of much free granular material which stained well with hæmatoxylin and masked the poverty of the myelinated sheaths (figs. 5 and 6). Particularly in the second case the demyelination was seen to be most marked in the neighbourhood of blood vessels and in this situation there was often the densest accumulation of large globular metachromatic bodies (figs. 7 and 8). The latter were also scattered diffusely throughout the white matter in better preserved as well as in the demyelinated areas. Some could be identified as microglial phagocytes, others contained no nuclei. Much metachromatic granular material also lay free in the tissues. Fibrous gliosis was a marked feature of the whole of the hemispheric white matter in the first case. In the second case gliosis was strikingly intensified in the perivascular areas of demyelination (figs. 9 and 10).

In the basal ganglia demyelination was present in the medullary striæ of the putamen and in the thalamus with the exception of the mammillothalamic and habenulo-interpeduncular tracts. The globus pallidus, the ansa lenticularis and the optic tracts were also relatively well preserved but contained abundant metachromatic bodies. The internal capsule, cerebral peduncles and medullary pyramids were severely affected but

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elsewhere in the brain-stem many tracts were only moderately or slightly demyelinated (fig. 11). The slightly affected tracts were the lemnisci, the central tegmental tract, the medial longitudinal bundle, the brachium conjectivum, the restiform body, the olivo-cerebellar fibres and the spinal trigeminal tracts. The pontocerebellar fibres and the tractus solitarius were more obviously damaged but retained a small proportion of their fibres.

In the cerebellum of both cases the central white matter was much more demyelinated than that of the folia or the hilum of the dentate nucleus. The central cores of the vermis and lateral lobes were diffusely and equally affected. In the spinal cord the spino-cerebellar tracts stained more strongly than the fibres of the posterior and anterolateral columns. The crossed and direct pyramidal tracts were severely degenerated and metachromatic material was mainly confined to these sites.

In all degenerating areas of the white matter oligodendrocytes were absent and astrocytic nuclei lacked their normal intensity of staining. While the metachromatic bodies were most numerous in the demyelinated parts they were also a conspicuous feature of many of the better preserved tracts.

Sections from a sciatic nerve showed that parts of the myelin sheaths of many fibres were broken up into small dark-staining globules but there was no severe demyelination. The Schwann cells contained abundant metachromatic lipid. Similar non-sudanophilic material was also present in large phagocytic cells (fig. 12).

TABLE II.—STAINING REACTIONS OF METACHROMATIC SUBSTANCE

Scharlach R	Pale buff
Sudan black B	Greyish-black
Nile blue sulphate	Deep blue
Kultschitsky-Pal's myelin method	Negative
Ziehl-Neelsen	Not acid fast
Fontana's ammoniated silver	Negative
Schmorl's ferric ferricyanide	Negative
Osmium tetroxide	Negative
PAS	Strongly positive
Alcian blue	Negative
Mucicarmine	Negative
Luxol fast blue	Positive
Toluidin blue	Strong gamma metachromasia
Hirsch-Peiffer's cresyl violet-acetic acid	Brown
Danielli's coupled tetrazonium	Negative
Millon's reaction	Negative
Feulgen's reaction	Negative
Methylene-blue extinction	pH under 0·6

Staining Reactions of the Abnormal Lipid

A series of histochemical staining reactions was carried out on sections of the cerebral white matter and of the brain-stem. The results are shown in Table II. In addition sections were extracted for twenty-four hours at room temperature with the following solvents: acetone, ethyl alcohol, a methanol-choloroform mixture, and pyridine. Metachromatic staining and staining with Sudan black was unaffected by acetone but disappeared after immersion of sections in the more powerful lipid solvents. It was apparent that abnormal metabolic products other than the metachromatic lipid were present in the tissues, for even after extraction with methanol-chloroform the globular bodies in the white matter stained strongly with PAS stain, while faint staining by this method was still shown by nerve cells belonging to nuclear groups in which metachromasia had been a prominent feature before lipid extraction.

Histology of Other Organs

In the liver metachromatic granules were seen in the epithelial cells of the intrahepatic bile ducts. Scanty periportal histiocytes also contained similar material. The epithelium of the gall-bladder showed similar changes to those found in the bile ducts. In the kidney abundant fine metachromatic granules were present in the epithelial cells of the loops of Henle, the distal convoluted tubules and the collecting tubules. Otherwise the organ appeared normal. In the adrenal numerous metachromatic cells occupied the medulla. The cortex was normal. The lung, spleen, lymph node, heart, thyroid and ovary and pituitary were normal and contained no metachromatic lipid.

Chemistry

Lipid analysis was performed on the cerebral cortex and white matter in both cases. The methods were those employed in previous papers (Tingey, 1956, 1959) with the following exceptions:

Cerebroside.—Neutral lipid galactose was estimated by a method modified after Radin *et al.* (1955) and the obtained value multiplied by 4·55.

Sulphatide.—Lipid sulphur was estimated by the benzidine method modified after Cuthbertson and Tompsett (1931) and expressed as cerebron sulphate after the formula of Folch *et al.* (1957).

Ganglioside.—Calculated from neuraminic acid after Svennerholm (1957).

The results are shown in Table III.

The significant abnormalities were confined to the white matter which showed a considerable increase of sulphatide. The myelin lipids cerebroside, sphingomyelin and cholesterol were considerably reduced.

The findings in both cases were remarkably similar and most of the

TABLE III.—LIPID ANALYSIS OF CEREBRAL CORTEX AND WHITE MATTER IN GRAMMES PER 100 GRAMMES DRY TISSUE

	Cortex				*White matter*			
	Normal adult	*Normal neo-natal*	*Case* 1	*Case* 2	*Normal adult*	*Normal neo-natal*	*Case* 1	*Case* 2
Total lipid	38·6	38·2	31·7	39·2	66·5	35·9	44·0	46·7
Cholesterol	5·1	4·9	5·5	5·6	12·0	5·6	7·8	8·4
Cholesterol ester ..	0·1	nil	0·4	nil	0·6	0·5	0·6	0·4
Total phospholipid ..	19·5	22·7	15·0	20·7	25·0	22·7	16·0	15·2
Lecithin	5·2	10·1	8·0	11·0	6·0	11·0	7·2	8·7
Sphingomyelin ..	1·7	0·2	1·3	0·1	2·6	0·5	1·4	1·5
Cephalin A	11·6	10·6	3·9	4·2	11·0	10·0	4·3	3·5
Cephalin B	1·0	1·8	1·8	5·4	5·4	1·2	3·1	1·5
Cerebroside (neutral) ..	2·42	0·73	1·46	1·14	9·23	1·22	3·59	3·51
Sulphatide	1·36	2·38	1·39	2·10	3·74	2·07	9·57	9·90
Ganglioside (N.A.) ..	1·84	1·22	2·10	2·01	0·52	1·72	0·42	0·70
Water	86·7	87·7	84·8	92·1	71·1	87·2	83·3	94·0

minor discrepancies can be ascribed to the effects of prolonged formalin-fixation in Case 1.

The kidneys of the two cases contained respectively 3·68 grammes and 3·62 grammes of sulphatide per 100 grammes of dry tissue as compared with 1·42 grammes found in a normal adult kidney.

Discussion

In the main features these 2 cases are typical examples of late infantile leuco-encephalopathy. The condition is well defined clinical and pathological entity and is probable commoner than the juvenile or adult variants (Greenfield, 1958). The characteristic pathological finding which distinguishes this group from other diseases in which progressive demyelination occurs is the predominant accumulation in the white matter and in the neurons of certain nuclei of a substance staining metachromatically with basic polychrome dues. In the late infantile cases there is also a remarkable disappearance of oligodendroglia not only from the more demyelinated and sclerosed regions but also from tracts which still retain many of their myelin sheaths. Strongly sudanophil lipid is only found in the walls of medium-sized vessels. It is, however, evident that the striking metachromatic lipid is not the only abnormal product of this disorganized myelin and cellular metabolism, for after its removal by appropriate solvents there remain large amounts of granular material staining positively with the periodic acid Schiff method. This substance or mixture of substances is present in the nerve cells showing metachromasia and in the large globular bodies of the affected white matter.

The metachromatic staining property of the abnormal lipid had already suggested the presence of sulphuric acid esters to Brain and Greenfield but several years elapsed before chemical proof was obtained by Jatzkewitz (1958) that this substance was sulphatide (cerebroside sulphate). Sulphatide has now been shown to be present in large excess not only in the brain but also in the kidney (Austin, 1959). In our cases the increased amount of this substance in the cerebral white matter has raised the value of total glycolipid to a relatively high level, the neutral cerebroside being in fact considerably reduced. The histochemical properties of the metachromatic lipid in the nerve cells are those of a sulphatide and are distinguishable from those of lipochromes in so far as the latter are acid-fast and have reducing properties. Doubts on this point have tended to retard the acceptance of the view that this disorder is a lipidosis rather than a primary demyelinating disease.

This resemblance to the neuronal storage diseases is strengthened by the histological features shown by our cases. The extent of the neuronal lipidosis is much more widespread than has hitherto been reported. The escape of the cerebral cortex and the involvement of the brain-stem,

spinal cord and some of the basal ganglia is a pattern of lesions also seen in the neuromuscular form of glycogen disease (Castaigne and Lhermitte, 1953).

Disappearance of nerve cells with or without evidence of storage in the remaining cells of the affected area is also a well known phenomenon in the lipidoses. Diffuse degeneration of the granular layer of the cerebellum as seen in our second case has often been described in the Batten type of amaurotic family idiocy and in this condition also it is not accompanied by evidence of storage in the surviving cells. The system-like pallido-Luysial degeneration found in both our cases was, however, associated with the presence of a moderate amount of metachromatic lipid in the remaining neurons. In other lipidoses we have suggested that focal loss of nerve cells may be attributed to the severity of the metabolic disturbance which kills the cells before they have time to accumulate abnormal products (Norman *et al.*, 1956). Perhaps the same process may be held responsible for the formation of the clefts seen in the claustra. These ragged cavities are not artefacts for they have been described in the same position by Wohlwill and Paine (1958) who also observed status spongiosus in the adjoining tissue.

Finally, it may be pointed out that severe demyelination is also found in Tay-Sachs' disease, particularly in patients surviving beyond the second year of life. This phenomenon cannot be adequately explained solely by the degeneration of cortical neurons and is evidently due in part to the abnormal lipid metabolism of the axons. It is generally held that in metachromatic leuco-encephalopathy the apparent primary degeneration of the oligodendrocytes is a factor of importance in the demyelinating process and the early disappearance of these cells may well be an expression of the enzymatic defect inherited in this disease. We have not been able to convince ourselves that the scanty oligodendrocytes in the less affected tracts stored metachromatic material but the Schwann cells of the peripheral nerves and the capsule cells of the posterior root ganglia certainly did so. The latter cells were regarded by de Castro (1932) as neuroglial cells similar in type to oligodendrocytes.

It thus appears that the condition is essentially the result of an inborn error of metabolism leading both to an intracellular and extracellular accumulation of lipids of which the prominent sulphatide component has now been identified.

The question still remains as to whether the visceral deposits of sulphatide are merely a "spill-over" from the nervous system or whether, as Witte (1921) originally maintained, their presence is due to a general metabolic disorder. The recognition of metachromatic leuco-encephalopathy as a form of neuronal lipidosis need not await the solution of this problem.

Summary

The clinical, histological and chemical features of late infantile metachromatic leuco-encephalopathy have been studied in 2 affected siblings. The recent discovery that the brain and kidney in this condition contain a large excess of sulphatide has been confirmed. The presence of this substance accounts for the metachromatic staining of the lipid found in the degenerating white matter, in peripheral nerves, in certain groups of nerve cells and in the epithelium of the renal tubules and intrahepatic bile ducts.

Sulphatide is not the only product of the metabolic disturbance present in this disease, for after removal of metachromatic lipid by solvents much granular material staining strongly with the periodic acid Schiff method remained in the tissues.

The present cases were remarkable for the selective involvement of the nerve cells of many of the brain-stem nuclei in the process of lipid storage.

Severe destruction of nerve cells had occurred in the globus pallidus, subthalamic nucleus and the claustrum, and in one case there was a diffuse atrophy of the granular layer of the cerebellum. It is suggested that this degenerative process is the result of a lethal intracellular metabolic defect and that the striking disappearance of interfascicular oligodendroglia in this disease may be due to a similar cause.

Many of these histological features are shared by one or another of the lipidoses. These similarities taken in conjunction with the evidence of the accumulation within the brain of a predominant lipid, namely sulphatide, provided good grounds for including metachromatic leuco-encephalopathy in the category of inborn errors of lipid metabolism.

Acknowledgments

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LEGENDS FOR PLATES

PLATE LI

FIG. 1 (*Case* 2).—Nucleus of facial nerve: abundant granules of metachromatic lipid are present in the nerve cells. Hirsch-Peiffer × 180.

FIG. 2 (*Case* 1).—Posterior root ganglion: metachromatic lipid is present in the ganglion cells and their capsule cells. Toluidin blue × 230.

FIG. 3 (*Case* 2).—Cerebellum: diffuse atrophy of granular layer with relative preservation of Purkinje cells. Carbol azure × 22.

FIG. 4 (*Case* 2).—Cerebellum: numerous swellings of Purkinje axons, diffuse loss of granule cells and astrocytic proliferation. Cajal's silver nitrate-pyridine × 110.

FIG. 5 (*Case* 1).—Right cerebral hemisphere (celloidin): the diffuse demyelination of the central white matter appears deceptively slight at this magnification. Heidenhain × 0·75.

FIG. 6 (*Case* 2).—Central white matter: very few myelinated fibres remain, but much granular material lies free in the tissue. Kultschitsky-Pal × 180.

PLATE LII

FIG. 7 (*Case* 2).—White matter of frontal lobe showing numerous metachromatic bodies. Toluidin blue × 64.

FIG. 8 (*Case* 2).—Parietal lobe showing characteristic distribution of metachromatic bodies around blood vessels and in arcuate fibres. Hirsch-Peiffer × 3.

FIG. 9 (*Case* 2).—Temporal lobe: the demyelination is most severe around blood vessels; note well preserved alveus (bottom right). Kultschitsky-Pal × 4.

FIG. 10 (*Case* 2).—As in fig. 9: perivascular gliosis in areas of severe demyelination. Holzer × 4.

FIG. 11 (*Case* 1).—Mid-brain: severe demyelination of cerebral peduncles with relative preservation of other long tracts. Kultschitsky-Pal × 1·2.

FIG. 12 (*Case* 1).—Sciatic nerve: metachromatic lipid is present in Schwann cells and in macrophages. Toluidin blue × 127.

PLATE LI

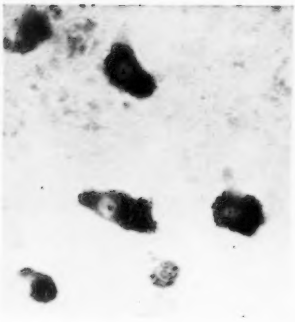

FIG. 1.

FIG. 2.

FIG. 3.

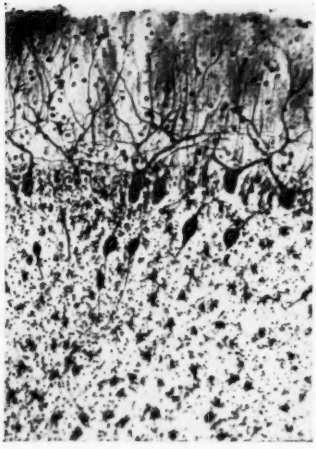

FIG. 4.

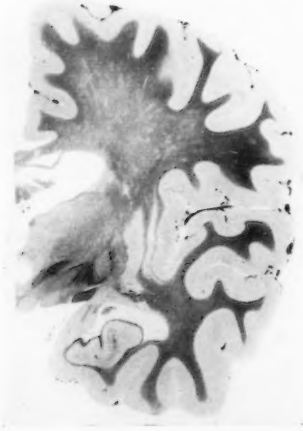

FIG. 5.

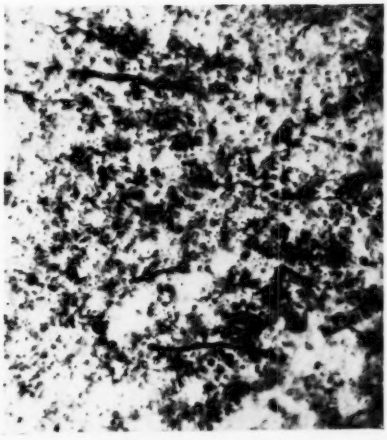

FIG. 6.

To illustrate article by R. M. Norman, H. Urich and A. H. Tingey.

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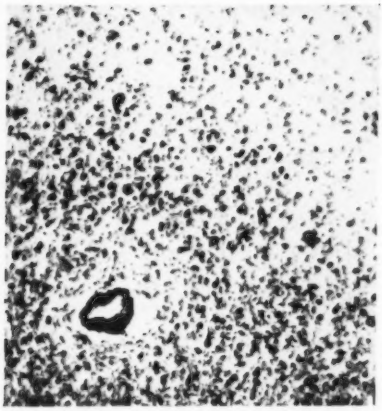

FIG. 7.

FIG. 8.

FIG. 9

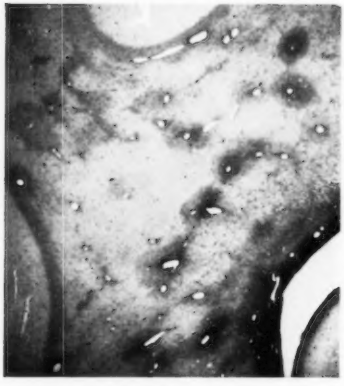

FIG. 10.

FIG. 11.

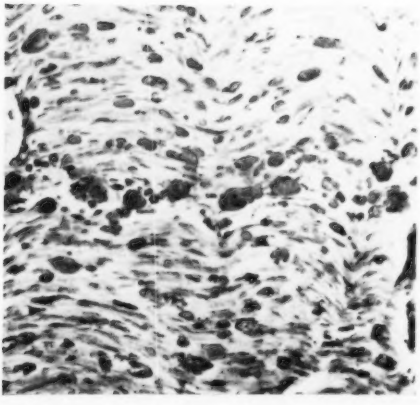

FIG. 12.

To illustrate article by R. M. Norman, H. Urich and A. H. Tingey.

CONGENITAL UNIVERSAL INSENSITIVITY TO PAIN

BY

D. W. BAXTER AND J. OLSZEWSKI

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INDIFFERENCE to pain though rare has been noted in a variety of circumstances. Persons under severe emotional stress, in states of great fear, or during episodes of conversion hysteria, may seem temporarily insensitive to injuries or stimuli which would ordinarily be accompanied by pain; and people who are mentally retarded and some who have a gross psychopathy react to painful stimuli much less actively than the normal. Morphine and related analgesic compounds produce states of *temporary* relative insensitivity to pain. Here the pain threshold is elevated but probably of even more importance is the dissociation between the appreciation of the painful stimulus and the patient's reaction to it. The same indifference to pain can be produced by frontal lobotomy. Again, the striking feature is the indifference to the stimulus. Adult patients have been described in whom an absolute or relative indifference to painful stimuli was first noted following a painless myocardial infarction or other visceral catastrophe. In retrospect, many of these patients recalled that previous episodes of skin trauma or dental extractions had been relatively painless (Jewesbury, 1951). Relative indifference to pain has also been reported infrequently in association with other disorders of nervous system function, most commonly in children with familial dysautonomia (Riley, 1957). Patients acquiring a vascular lesion in the supramarginal gyrus of the dominant hemisphere may show an asymbolia for pain as part of their parietal lobe symptomatology (Schilder and Stengel, 1928, 1930; Schilder, 1931; Pötzl and Stengel, 1936).

Standing clearly apart from all of these, although not necessarily unrelated to them, are those cases usually described under the heading of congenital universal indifference or insensitivity to pain. Although thought to be present from birth, this condition is not usually diagnosed until the child is old enough to move about unaided, by crawling or walking. It is then noted that it does not cry following injuries and fails to learn to appreciate what forms of stimuli are damaging to tissue and usually

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painful. Boyd and Nie's (1949) patient suffered a fracture dislocation of her elbow at the age of 1 year, and yet showed no evidence of pain and continued to use the extremity. Later, she suffered severe burns by leaning against a hot stove and when questioned regarding pain in the burned areas replied that they felt "warm and good." As these children grow older they show the consequences of their indifference to tissue damaging stimuli. By the age of 7 or 8, their extremities may show the scars of many cuts, abrasions and burns. Some will have chewed off the end of their tongue or picked away portions of their nose. They show deformities resulting from their painless fractures. After the age of 7 or 8, their injuries become more infrequent—apparently not due to any increased appreciation of pain but rather that they learn what forms of stimulation are likely to cause skin and bone injuries. They may pass their intellectual and motor landmarks normally and do well at school. They rarely, if ever, experience headache, toothache, earache or visceral pain. One patient claimed to have experienced no pain during labour (Madonick, 1954). In most instances their speech has been normal but Ford and Wilkins (1938) reported one such child who stuttered and another who had a specific reading disability. Examination of muscle power, strength and co-ordination show no abnormalities. Deep tendon reflexes are brisk and plantar responses flexor. No defects in visual function, such as colour blindness, have been noted and in only a few cases have there been an associated loss of taste and smell (Madonick, 1954; Grain, 1949). The corneal reflex is absent or reduced and they report a sensation of touch rather than pain when the cornea is stimulated. The sensation of nose tickle is usually absent and the gag reflex may be depressed. The appreciation of touch, vibration sense and joint position sense is normal. Although they fail to appreciate pain, they can distinguish between sharp and dull and warm and cold. Stereognosis is normal or slightly impaired.

These patients have been subjected to various forms of painful stimuli under carefully controlled conditions. They usually report no sensations of pain or, at most, a mild discomfort following prolonged stimulation by muscle ischæmia, intramuscular hypertonic saline, local heat, or local cold (McMurray, 1950). No patient has been reported in whom a histamine headache could be produced and no cases of post-pneumoencephalographic headaches have been recorded. Autonomic responses to painful stimuli are present in some patients but absent in others (McMurray, 1950; Jewesbury, 1951; Madonick, 1954; Kunkle and Chapman, 1943). The histamine flare is said to be normal. Several of these patients have had skull films, E.E.G.s and pneumoencephalograms. No abnormalities have been reported except in the occasional case where there was an associated convulsive disorder (Jewesbury, 1951).

Jewesbury (1951) also reported the case of a 16-month-old boy who

appeared to be grossly indifferent to pain and who yet developed normal responses after the age of 2½ years. In all other reported cases there was no change in the nature or severity of the perceptual defect during the period of observation.

There has been much discussion regarding the probable morphological substratum of these cases (Critchley, 1934, 1956; Ford and Wilkins, 1938; Boyd and Nie, 1949; Jewesbury, 1951; Von Hagen, 1949). To date no autopsy studies on a typical case of congenital universal indifference to pain have been reported. In 1955 Biemond did report, in an abstract, the autopsy findings in an 11-year-old boy who had showed a complete analgesia of his entire body. There were, however, several features which make it difficult to accept this case as a typical example of insensitivity to pain. Both of the child's feet were deformed, he was permanently incontinent and he was deaf and dumb. He was initially regarded as an imbecile although Biemond thought that he was not. Examination of his brain and upper cervical cord revealed marked hypoplasia of the posterior columns and marked cell loss in the dorsal horns of the spinal cord. The spinal trigeminal complex of the brain-stem was hypoplastic and almost devoid of cells. In the thalamus there was some cell loss in the ventromedian nucleus and the parietal operculum of the cortex was underdeveloped. These findings are in marked contrast to what we are about to report.

Clinical History F.C.

This patient was born in Canada and was the daughter of a physician. Her apparent insensitivity to pain was noted from a very early age. She was described as highly excitable and subject to temper tantrums as a child. She bit her tongue on many occasions, so that the tip of the tongue was permanently deformed. In her temper tantrums, she would bang her head against the floor, and on several occasions large hæmatomas formed. At the age of 21 months, she was admitted to a hospital for incision of a large soft abscess over the occipital bone. The hospital notes at this time comment that the child did not appear sensitive to pain. Also, it was noted that she would bruise and cut her extremities without showing any evidence of experiencing pain. At the age of 3 years, she was hospitalized because of an osteomyelitis of the right calcaneus. During the same year, she sustained a third degree burn on her right leg while kneeling on a hot radiator watching other children play outside the window. Again, there was no complaint of pain.When 8 years of age, she was hospitalized on four occasions. One was for an acute pyelitis, and three were for treatment of osteomyelitis which had developed at the lower end of both femurs. The notes repeatedly mention that the child did not complain of pain.

By this time, the patient was aware of her peculiar insensitivity to tissue-damaging stimuli. She became sunburned on several occasions and noted that in contrast to her friends, the affected area never caused her discomfort. On one occasion, she had an attack of the hives but denied ever having experienced the sensation of itching. She denied any history of headache, earache, toothache, stomach ache, or dysmenorrhœa. She had learned to inspect her feet after a day at the beach to be sure that she had not sustained any unnoticed lacerations. Her extremities were frost-bitten on several occasions during the winters, but this was not associated with pain.

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When 17 years of age, she was admitted to hospital complaining of "loose particles around the left knee-joint which bothered her and she wanted them removed." Examination of the knee revealed three loose bodies palpable in the suprapatellar bursa. Although marked crepitation was elicited by flexing or extending the joint, the range of movement was normal. Examination of the spinal column at this time revealed a moderate thoracolumbar kyphosis. No pain was elicited on percussion over the spinous processes. X-rays of the vertebral column showed a gross kyphosis in the upper lumbar area and a beginning thoracic kyphosis at the level of T7. Multiple lower thoracic and upper lumbar vertebræ were partially destroyed, and there were calcareous deposits along the psoas shadows bilaterally. The X-ray appearances were interpreted as probably being the result of tuberculous infection of the vertebral bodies plus psoas abscesses. X-ray examination repeated a few months later was said to show definite evidence of healing of these lesions.

At the age of 22 years, the patient was admitted to the Montreal Neurological Institute for neurological evaluation. It was at this stage, too, that she was extensively studied by Dr. McMurray (1950). Dr. F. McNaughton's neurological examination is quoted by Dr. McMurray as follows: "The cranial nerves are normal except for the following observations: In tests for the corneal reflex, there is occasionally a very slight movement of the eyelids when the cornea is touched, and it is difficult to be sure that this is not a reaction to an approaching and threatening object. With the ordinary method of testing, one would say that the corneal reflex is absent on both sides. The patient does feel very light touch on the conjunctiva, and possibly on the cornea as well. On her face and elsewhere on the body she can distinguish between the touch of the finger alone and the touch of the finger associated with pin-prick. At first, she thought I was digging in with a finger nail and said that she simply felt something sticking into the skin but that she experienced no pain with it. The same is true when a hypodermic needle is inserted into the epidermis. She feels it penetrating the layers but experiences no pain. Supra-orbital pressure with the finger causes no discomfort whatsoever. A stick can be inserted up through the nostrils without causing any discomfort or tendency to sneeze or withdraw. The same is true when the external auditory canals or the drum membrane is touched lightly with a stick. There is no tickling sensation from either nasal orifice. The gag reflex can be elicited only by stimulating low down on the posterior pharyngeal wall.

"There is fair muscular development and no localized wasting or weakness, and tests of co-ordination are well performed with either hand or arm.

"The deep reflexes are normally active and equal on the two sides. The abdominal reflexes are active and equal, and the plantar responses, while slight, seem to be flexor in type.

"Her ability to distinguish between touch alone and touch associated with pin-prick has already been noted. There is no reaction to heavy pressure on the Achilles tendon of either leg. She can appreciate even very weak vibration, as tested with a tuning fork. Position sense in the toes also seems perfectly normal.

"She is able to distinguish between hot and cold objects anywhere on the body surface, even when the difference between the two temperatures is not great.

"The ciliospinal reflex was tested, but no definite change was noted. There are frequent alterations in diameter of the pupil at all times.

"Summary: Examination does not reveal any evidence of organic neurological disease, such as syringomyelia. There are several bony deformities which have resulted from osteomyelitis. The lateral malleolus of the left leg is abnormally large, though she has never had osteomyelitis of this region, suggesting the possibility of a Charcot joint. However, there is no unusual mobility or crepitus of this joint. There are no trophic changes in the fingers or toes and no unusual scars or calluses on the feet. The

remarkable feature is the complete absence of any experience of pain at all or of the usual reactions to it.

"Histamine test: The subject was given 0·1 c.c. of a 1 : 1,000 solution of histamine phosphate intravenously, producing slight taste sensation in the mouth, throbbing sensation and specks before the eyes. At the same time, there were increased pulse-rate and throbbing of the arteries in the neck. Headache was not produced."

An electroencephalogram done at this time was normal. The residents' notes on this hospitalization also comment that the tip of the patient's tongue was bitten off and that she could perform "all sorts of acrobatic movements easily and without any discomfort."

One year later, at the age of 23, she noticed that she was beginning to limp and that her right hip-joint was becoming stiff. Examination then revealed that the right leg was 2 in. shorter than the left, that there was marked crepitation on movement of the right hip-joint, and that there was a fluctuant swelling just below the right anterior iliac crest. Note is also made at this time that the patient was able to dislocate both her shoulders and voluntarily replace them easily. X-rays showed loss of substance in the right acetabulum and in the femoral head. A shelf operation was done but did not correct the limp.

In January 1951, at the age of 24, she first noticed some difficulty in climbing stairs. At this time, she was taking a psychology course at McGill and enjoying an active social life. Within a few weeks, she found that she was unaware of where her feet were and that both feet and legs felt numb. Muscle weakness in the lower extremities progressed until she had considerable difficulty walking. Later she began experiencing frequent flexor spasms involving both lower extremities and developed occasional urinary and fæcal incontinence. At no time did she give any history of back or girdle pain. She was admitted to hospital in March of 1951 and during the next two months showed very slight progression of her symptoms. In May, a myelogram was done, showing an almost complete block at the level of T11. The cerebrospinal fluid on this occasion was clear and colourless, and contained 20 lymphocytes per c.mm., and a protein of 68 mg. per cent. Following this myelogram, she was again investigated at the Montreal Neurological Institute. The following information is abstracted from notes made at that time by Dr. J. Bates.

There was a marked kyphosis of the lower thoracic and upper lumbar region, with a scoliosis to the left. The skin over the prominent spinous processes showed thinning and reddening. There was no tenderness on percussion over the spinous processes. The patient was able to manipulate herself with great agility, in fact excessively so. There was considerable abnormal movement in the lower thoracic spine. She was alert and intelligent. Dr. Bates felt that she "tended to be rather jovial about the whole business and in fact was not very anxious to consider the situation seriously." Examination of the cranial nerves revealed no changes from the findings recorded previously by Dr. McNaughton. There was moderate weakness of all movements of both lower extremities, with increased tone in these limbs. Deep tendon reflexes were hyperactive in the lower limbs, with bilateral ankle and knee clonus. The plantar responses were extensor. The sensation of touch was intact over the entire body. To pinprick there was a definite sensory level at T11 on the right and at T12 on the left. Above this level she was able to distinguish sharp from dull and described deep pin-pricks as unpleasant. Loss of reaction to pin-prick was maximal over the dermatomes of T12 to L4, and less marked over the L5, S1, S2 dermatomes. Sharp could be distinguished from dull in the S3, S4, S5 dermatomes. This gradient was similar on both sides. Hot and cold could be distinguished at all levels, but these sensations were less intense below the T12 dermatomes. Vibration sense was present at the anterior iliac spines but absent elsewhere in the lower extremities. Joint position sense was absent in the great toes.

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A decompression of the spinal cord at the level of T10–11 was done by Dr. Cone in May 1951. "An adequate decompression was achieved by removal of what seemed to be granulation tissue from the extradural space, as well as by removal of altered bone and intervertebral disc tissue." A spinal fusion was then done between T7 and L1. Microscopic examination confirmed the gross impression of granulation tissue. Following this procedure, slight improvement occurred in that the sensory findings were less marked. No return of motor power occurred. A urinalysis done during this hospital admission was reported to be protein free.

The course between 1951 and 1955 is summarized by Dr. Macgregor as follows: "Early in December, 1951, Miss C. again began to notice increasing weakness and loss of control of her legs while walking. It was felt that some pressure was present at the site of the previous spinal operation. On December 11, 1951, a bilateral decompression laminectomy from D9–D11 was carried out, followed by a repeat fusion using an H graft consisting of a split, refrigerated rib. The patient had an uneventful post-operative course except for spasms in her legs which lasted for several weeks.

"She was readmitted to the University of Alberta Hospital on August 12, 1952, with malaise and an infected tooth. Examination disclosed induration of soft tissues in the region of the old scars about the right hip. She had recurrent bouts of pyrexia and there was little response to massive antibiotic therapy. The right hip-joint subsequently became fluctuant and was aspirated, on several occasions, during 1953. In May 1953, the right hip-joint was incised and drained. Dislocation of the right hip was encountered together with a large false joint, and chronic suppurative synovitis. In June 1953, Miss C. was treated for urinary tract infection, due to *Streptococcus viridans*. During an admission in August 1953, a diagnosis of secondary amyloidosis was established on the basis of a congo-red test which yielded a value of 85 per cent retention of dye, as compared with a normal value of up to 35 per cent.

"In July 1955, Miss C. presented with a spiking fever, nausea, vomiting and discomfort in the region of her left hip. The latter was found to be swollen and tender. Radiologically, there was evidence of partial subluxation of the left hip, accompanied by destruction of the left femoral head. The urine contained 3 and 4 plus protein. The maximum urinary concentration was to a specific gravity of 1·014. It is of interest that during this admission, the patient complained of pain in the region of her left hip and that this was relieved by Frosst's 292 tablets. The left hip was drained surgically. Bacteriological studies yielded *Staphylococcus aureus*. A number of cultures for tubercle bacilli were negative. One culture, however, taken on August 17, 1955, from the left hip yielded a growth of acid-fast bacilli after five weeks of culture, on Loewenstein's medium. A guinea-pig inoculated with the same specimen remained in good health. A second guinea-pig was inoculated from the culture of acid-fast organisms but this subculture failed to grow in the animal. For this reason, we feel that there is some doubt as to whether there was a tuberculous component to the patient's left hip infection.

"The patient's final admission to the University Hospital was on August 28, 1955, because of diarrhœa, persistent vomiting, cough, dyspnœa, weakness, and confusion, apparently of ten days' duration. She also complained of "blackouts" and blurring of vision. Physical examination at that time revealed an ill-looking, young woman, who was tossing restlessly in bed. Her conversation was somewhat incoherent. She seemed breathless at rest, with audible wheezing, and repeatedly coughed up small amounts of sputum. Objectively, cranial nerves were intact, speech was loose and slurred, rhonchi were heard diffusely throughout both lung fields, coarse rales were also present in both lung bases, respiration was laboured, with prolongation of the expiratory phase; there was slight generalized tenderness on palpation of the abdomen; no organs or masses were palpable, however. Pulse was of poor volume but was regular at 80 per minute. Blood pressure was 95/55 mm. of mercury.

"Laboratory investigations: Hb. concentration—6·7 grammes per cent. Sedimentation rate 22 mm. per hour, corrected. The total white blood count was 17,700 with a neutrophilic granulocytosis. Urine contained three plus protein and two plus sugar, as well as many pus cells, occasional red cells and many bacteria.

"Despite supportive therapy, death occurred at 6.15 p.m., August 30, 1955."

This patient has been the subject of three previous reports in the literature. In 1950 Dr. Gordon McMurray reported the results of an extensive series of psychological and physiological tests. He found her Wechsler Bellevue Intelligence Scale showed a verbal I.Q. of 119, a performance intelligence quotient of 132, and a full-scale intelligence quotient of 128. Her Wechsler Memory Scale quotient was 106. The Rorshach Test, the Thematic Apperception Test, the Cornell Index, and McFarland's and Seitz's Psychosomatic Inventory revealed no gross personality disorders.

Attempts were made to determine the patient's threshold for warmth and pain using the Hardy-Wolff apparatus. The threshold for warmth was slightly elevated. Attempts to determine a pain threshold were hampered by the fact that she failed to complain of pain despite the use of strong enough stimuli to cause skin blistering. Attempts to induce pain by exercising ischæmic muscles of a forearm and hand also failed.

Several experiments were carried out to determine whether or not she developed normal physiological responses to noxious stimuli. Stimuli included immersing the right hand in water at 0–2° C. for eight minutes, immersion of the hand in water at 49–51° C. for five to eight minutes, and a series of electric shocks applied to the skin of the forearm. In response to these stimuli all of the normal controls complained of pain, appeared and behaved as though in pain, showed a rise in blood pressure and pulse-rate, and a disturbance of the respiratory rhythm. The patient did not complain of pain, appear to be in pain, or show any significant change in pulse-rate, blood pressure, or respiratory rhythm when subjected to the same stimuli. In contrast, she showed the expected normal variations in blood pressure when subjected to stressful psychological tests which did not make use of physically noxious stimuli.

Petrie (1953) described the orthopædic complications which this patient developed. He pointed out the probable importance of the loss of pain sensation as the ætiological factor responsible for the neuropathic joint disease. During one of the orthopædic procedures which this patient required, specimens of skin, fascia, periosteum, bone and cartilage were obtained. These specimens were studied by Feindel (1953) in an attempt to demonstrate free nerve endings which are usually considered to represent the terminations of pain fibres. "In the specimens of skin there were nerve bundles containing up to as many as seventy nerve fibres, including fibres of medium diameter and fine non-myelinated fibres. More superficially these bundles gave off smaller leashes of fibres which formed a

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sub-epithelial plexus. Myelinated fibres could be traced to a point where they divided to give fine non-myelinated fibres, having a characteristic beaded appearance. These in turn each supplied a superficial network of free-ending naked terminals which stood out clearly against the pale-staining epithelium. The most superficial and distal fibrils of the network were usually single with loops or branching formations. The deeper branches were multiple and intermingled with adjacent terminals from other fibres. One end-organ was seen which was made up of a complex skein of terminals resembling a thermal receptor.

"In periosteum no large nerve bundles were seen and the density of innervation was less than that of the skin. Bundles containing up to four nerve fibres were present. One fine fibre was seen bifurcating to supply beaded free terminals alongside a small blood vessel, although no arborizing networks were noted as in the skin.

"In the specimens of superficial and deep fascia, bone and cartilage no nerve fibres were seen, but staining of these samples was unsuccessful." As a result of these studies, Feindel concluded that "From the histological evidence available, it seems probable that the defect in the perception of pain and in the reflex protective effects of pain in this subject lies in central rather than in peripheral nervous structures."

Autopsy Findings

The autopsy was performed under the direction of Dr. J. W. Macgregor, Professor of Pathology at the University of Alberta, Edmonton.

The body was that of a moderately well-developed and nourished young adult female of slight build, measuring 65 in. in length, and weighing approximately 105 lb. Multiple scars and joint deformities were noted. The right ankle was arthrodesed and fixed in plantar flexion. The left ankle-joint was disorganized and had the external appearance of a Charcot joint. The left knee was swollen and there were two old, healed para-patellar scars. There was an old linear incisional scar measuring 10 cm. in length which occupied the lower third of the medial aspect of the left thigh. Its superior margin was continuous with a chronic cutaneous ulcer, with sloping edges and a necrotic base measuring 2 cm. in diameter. The left hip-joint was hypermotile. Over the posterolateral aspect of the left buttock, there was a saucerized draining sinus tract. Examination of the right hip revealed an old incisional scar measuring 50 cm. in length, extending from the right sacrum along the iliac crest to the junction of the middle and upper thirds of the right thigh anteriorly. There is an old vertical scar in the mid-line of the back from D5 to L2. There were many circular, oval, and linear scars ranging from 1 to 5 cm. in diameter on the low back, right thigh, sacrum, buttocks and right tibia.

The organs of the thorax and abdomen were found to be normally disposed. The left and right lungs weighed 570 and 560 grammes respectively. The major portion of each lower lobe was consolidated and of fleshy appearance. Multiple cross cuts revealed appearances compatible with a patchy and confluent bronchopneumonia. A moderate amount of pus could be expressed from the smaller radicles of the bronchial tree. The heart weighed 250 grammes. The cardiac chambers were not dilated or remarkable. The valve cusps were normal. The aorta and other vessels were free, of atherosclerosis. In the abdomen, many fleshy grey lymph nodes averaging 1 cm. in diameter were demonstrable along the base of the mesentery, at the hilus of the liver

and spleen, and in the periaortic area. The spleen weighed 350 grammes, and cross sections revealed many prominent grey nodules which stained intensely with Lugol's iodine. The left and right kidneys weighed 350 and 370 grammes respectively. The capsule was smooth and shiny but stripped with some difficulty. Cross section revealed thickening of both the cortex and medulla, with partial replacement, particularly in the cortex, by material of firm consistency and yellowish-brown waxy appearance. This, too, stained a mahogany brown colour with Lugol's iodine. Multiple saw cuts through the bodies of vertebræ from D10 to L3 revealed marked distortion with condensation and osteophyte formation. Beneath the outer dense cortical layer, spongy bone could be demonstrated supporting normal red marrow. The vertebral bodies of D10 and D11 were partially collapsed. The liver weighed 2,100 grammes. Cross sections revealed preservation of lobular architecture, but some hepatic tissue was replaced by a homogeneous grey material which stained with Lugol's. External examination of the stomach, œsophagus, pancreas, adrenals, and gall-bladder was normal. Microscopic examinations confirmed the gross diagnosis of bronchopneumonia and amyloidosis of the liver, spleen, pancreas, adrenals, kidneys, and lymph nodes.

Dr. Macgregor kindly allowed us the opportunity to study the neuropathological material in detail.

In its fresh state the brain weighed 1,300 grammes. The dura and arachnoid were unremarkable, and the cerebral vessels were free of atherosclerosis.

The gross appearance of the brain was normal. There was no evidence of generalized or focal atrophy for which the frontal lobes, parietal opercula and post-central gyri were examined particularly. From each cerebral hemisphere a block containing the entire thalamus was removed. The remainder of the hemispheres were then sectioned coronally. The configuration of the ventricles was normal. The cortex was of usual width and configuration. No gross lesions of the white matter were seen. Multiple blocks from the frontal, sensorimotor, parietal, temporal and occipital areas of both hemispheres were prepared for histological study. These were stained by Nissl and Heidenhain methods. These sections showed normal cyto-architecture and myelo-architecture of all the areas studied. Fig. 1 (Plate LIII) shows a representative portion of cortex from the post-central gyrus.

Serial sections were made through the entire length of right and left thalami. Alternate sections were stained with Nissl and Heidenhain techniques. These were studied in detail, and no abnormalities of nuclear configuration, cyto-architecture or myelo-architecture could be demonstrated. Fig. 2 shows a myelin stained coronal section of the thalamus at the level of the nucleus ventralis posterior. The medial, lateral and inferior portions of this nucleus are clearly seen and are of normal size. The normal cyto-architecture of the nucleus ventralis posterolateralis and nucleus ventralis postero-inferior are illustrated in fig. 3.

The gross appearance of the lower brain-stem and cerebellum was unremarkable. The brain-stem was separated from the cerebellum and sectioned serially. Alternate sections were stained for cells and myelin. No abnormality of microscopic structure could be demonstrated at any level (figs. 4, 5, 6 and 7A). Particular attention was paid to the sensory components of the trigeminal system. The cellular structure of the main sensory and the spinal trigeminal complex was normal. Figs. 7B and C illustrate the normal myelo- and cyto-architecture of the caudal spinal trigeminal nucleus. The spinal trigeminal tract was well myelinated, of usual size and could easily be demonstrated at all levels between mid-pons and caudal medulla.

The spinal cord and nerve roots seemed smaller than average, but we have not yet been able to compare them with those of a patient similar in age, size and weight (fig. 8A). Cross sections were made at various levels of spinal cord and stained by H and E, Nissl and Heidenhain methods. Cross sections through the upper lumbar cord showed

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diffuse demyelination of all columns (fig. 9). This area presumably corresponds to the site of spinal cord compression by the extradural mass of granulation tissue (*see* clinical history). All sections of the cord above this level showed the changes of ascending degeneration (figs. 8B and C), and sections of the sacral cord showed evidence of descending degeneration (fig. 8D). Sections of the lower thoracic cord (fig. 8C) show degenerative changes both in the posterior column and in the areas occupied by the spinothalamic and spinocerebellar tracts. More rostral sections through the brainstem (figs. 7, 6, 5 and 4) fail to show any evidence of degeneration in the area thought to be composed of spinothalamic or spinocerebellar fibres. The myelo-architecture and cyto-architecture of the dorsal horns of the spinal grey matter were normal at all levels except at the site of compression. In the root entry zone the distinction between the heavily myelinated medial fibres which enter the dorsal columns and the finely myelinated lateral fibres which enter the tract of Lissauer, can be easily made (fig. 10).

Sections were made of both dorsal and ventral roots at several levels in the cervical, thoracic and lumbar regions. These sections were stained with osmic acid and Schmidt silver stain. Fig. 11 shows a typical cross section through a dorsal and ventral nerve root. The proportion of small fibres is much greater in the dorsal than in the ventral root, and the majority of these small fibres measure less than 3 microns in diameter. Comparable sections stained with silver show the presence of an even greater number of small fibres in the dorsal root than the myelin stained section would indicate—thus demonstrating the presence of very finely, or so-called unmyelinated fibres (fig. 12). Similar fibres are easily demonstrated in each of the several peripheral nerves examined (fig. 13). Sections of dorsal roots, ventral roots and peripheral nerves from this patient were compared with many similarly stained control sections. We were unable to notice any significant difference in the proportion of small and large fibres in comparable sections. The value of attempting to chart spectra of fibre sizes in the dorsal roots of this patient was considered. However, since it appeared obvious that no great departure from the average would be found and that the interpretation of minor variations would be difficult, this approach was abandoned.

No dorsal root ganglia were available for study.

Discussion

We began our study of this patient with the assumption that pain was a specific sensation, the anatomical pathways for which were reasonably well defined. We felt that if this syndrome had a morphological substratum this might be found by careful examination of those parts of the nervous system thought to be concerned with the transmission and elaboration of pain impulses. However, no abnormalities of these structures could be demonstrated.

Feindel's (1953) study showed that this patient possessed the fine, freely ending nerve terminals which are usually considered to be pain receptors. This has been confirmed in skin biopsies from other patients with congenital insensitivity to pain (Kipnis *et al.*, 1954). Our studies show the presence of a normal number of finely myelinated and "unmyelinated" fibres in the peripheral nerves and dorsal roots. Such fibres are thought to be concerned with the transmission of pain impulses towards the central nervous system. Unfortunately, the cell bodies of these fibres could not be studied as no dorsal root ganglia were obtained at the time of autopsy. However, in the presence of normal peripheral nerves, dorsal roots and

dorsal columns, we can assume that these structures too were normal—with the possible exception that the number of cells might have been less than average.

Those anatomical structures of spinal cord and brain-stem concerned with the transmission of pain impulses were also normal. Finely myelinated fibres could be seen separating off from the more heavily myelinated proprioceptive and touch fibres, to form the tract of Lissauer—and in the brain-stem the spinal trigeminal tracts were quite normal. These fibre tracts terminate by synapsing with the cells of the dorsal horn of spinal grey matter and subnucleus caudalis of the spinal trigeminal complex. These structures, too, were normal.

We are able to say very little concerning the integrity of the spinothalamic and quintothalamic tracts. Although these structures occupy fairly well-defined areas, their fibres lie intermingled with those of other fibre systems. If they were completely demyelinated, it is probable that this could be recognized. On the other hand, it is conceivable that it would not be noticeable if the tracts were altogether absent. If there was a spinothalamic tract in this patient, those fibres below L2–3 presumably contribute to the area of ascending demyelination in the lateral portions of the spinal cord. It is our impression that there is more extensive demyelination present than one would expect in ascending degeneration restricted to the spinocerebellar systems.

The exact mode of termination of the spinothalamic and quintothalamic tracts is not known. It is probable that at least some of these fibres proceed all the way to the thalamus. However, the number of fibres in the spinothalamic tract at the level of the upper brain stem is said to be very small (Glees, 1953). Thus, some workers (Walker, 1940) have postulated that a proportion of fibres may synapse with the cells of the reticular formation before proceeding to the thalamus and others have suggested that the most oral portion of this tract is unmyelinated (Gardner and Cuneo, 1945). The portions of the thalamus which receive the exteroceptive impulses are nucleus ventralis posterolateralis and nucleus ventralis posteromedialis. According to some authorities, the pain fibres terminate predominantly in the nucleus ventralis postero-inferior (Hassler, 1948). All these structures were normal.

The role played by the cortex in the appreciation of pain has long been the subject of controversy. Since the classical studies on cortical sensation by Head and Holmes (1911) most clinical neurologists have accepted the dictum that pain impulses enter consciousness at the thalamic level and that the cortex is not essential for the appreciation of pain. This view is supported by considerable physiological and clinical data (Biemond, 1956). On the other hand, there always have been serious objections to this view. The considerable clinical data which would emphasize the role of the cortex in the appreciation of pain are detailed in the papers of Marshall

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(1951) and Biemond (1956). Biemond's (1956) clinicopathological studies have led him to suggest that the region of the parietal operculum may be a cortical centre for pain, receiving fibres directly from the ventralis posterior complex of the thalamus. Kleist (1934) suggested that lesions far forward in the parietal lobe are liable to result in disturbances in the appreciation of pain, whereas loss of joint position sense and stereognosis were usually associated with lesions lying more posterior in the parietal lobe.

Thus, in any study of the anatomical pathways of pain conduction, the main interest would centre around the parietal opercula, the post-central gyri, and the adjacent anterior parietal cortex. These areas were studied in detail and no abnormalities of myelo-architecture, cell form, size or distribution could be found. Multiple sections of frontal, temporal and occipital lobes were all found to be normal. No definite comment can be made regarding the thalamocortical connexions. The exact course which these fibres take is unknown and the absence of those concerned with pain (if indeed such exist) would probably not be noticeable. All we can say is that the white matter lying between thalamus and cortex showed no gross abnormalities.

We have failed, therefore, to demonstrate any anatomical abnormalities of those nervous system structures thought to be concerned with the transmission, elaboration and perception of pain impulses. We cannot, however, exclude the possibility that the defect is actually an anatomical one, but either submicroscopic or in terms of organization rather than structure. For example, even a small variation in fibre size might so distort the temporal and spatial pattern of impulses that they would not be interpreted as pain on reaching the thalamus or cortex. Alternatively, the same physiological consequence might result from malposition of the nodes of Ranvier or from distortion of normal synaptic relationships. It is equally possible that the defect should be considered a perceptual one and related to other congenital gnostic defects such as developmental alexia. Finally, it must be realized that there are great variations in the intensity with which so-called normal individuals appreciate pain—and that states such as fear may nullify the effects of painful stimuli. If we accept these variations in pain appreciation without expecting to find anatomical alterations, then it is possibly not surprising to find certain rare individuals who consistently fail to appreciate pain and who also have normal anatomical pathways. It may well be that there are degrees of insensitivity to pain of which our patient was only an extreme example.

Summary

We have presented the autopsy findings of a young woman who suffered from congenital insensitivity to pain. Her lack of pain appreciation was so great that she suffered extensive skin and bone trauma which contributed in a direct fashion to her death. Yet we were unable to demon-

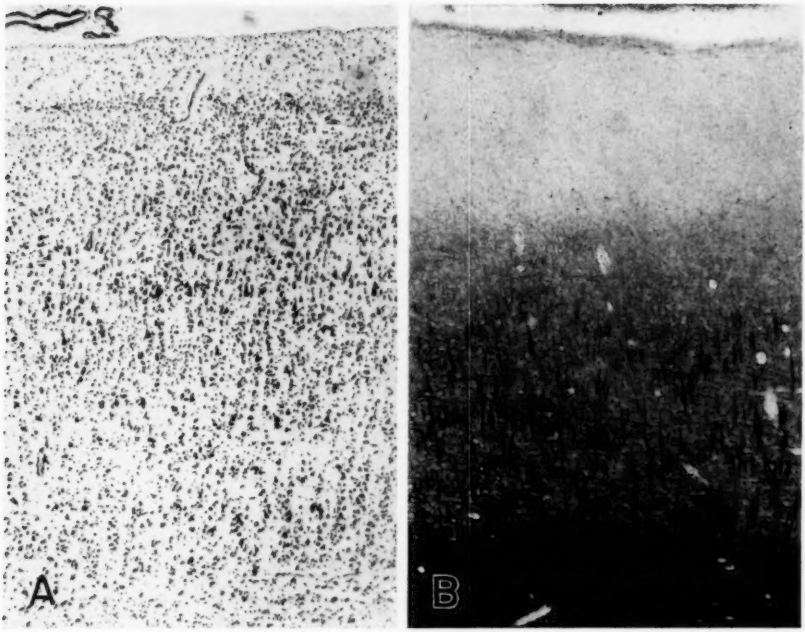

FIG 1.—Post-central gyrus. Nissl and Heidenhain stain. ×30.

FIG. 2.—Coronal section of the thalamus. Heidenhain stain.

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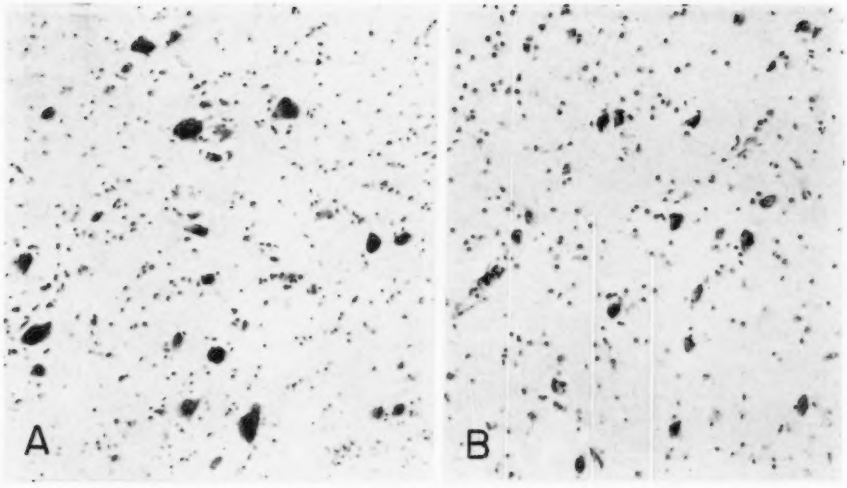

FIG. 3.—A, Nucleus ventralis postero-lateralis and B, Nucleus ventralis postero-inferior. Nissl stain. ×165.

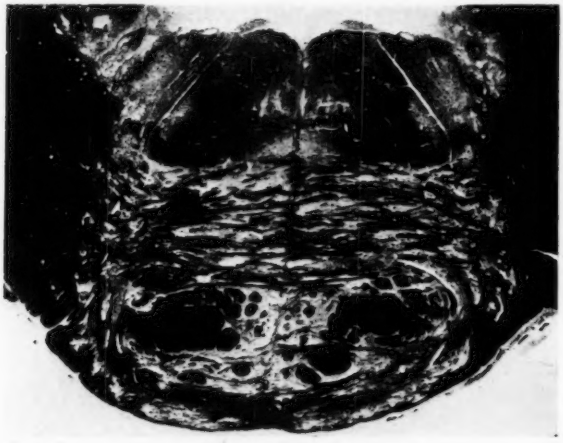

FIG. 4.—Cross section through the pons. Heidenhain stain.

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FIG. 5.—Cross section through the ponto-medullary junction. Heidenhain stain.

FIG. 6.—Cross section through the medulla. Heidenhain stain.

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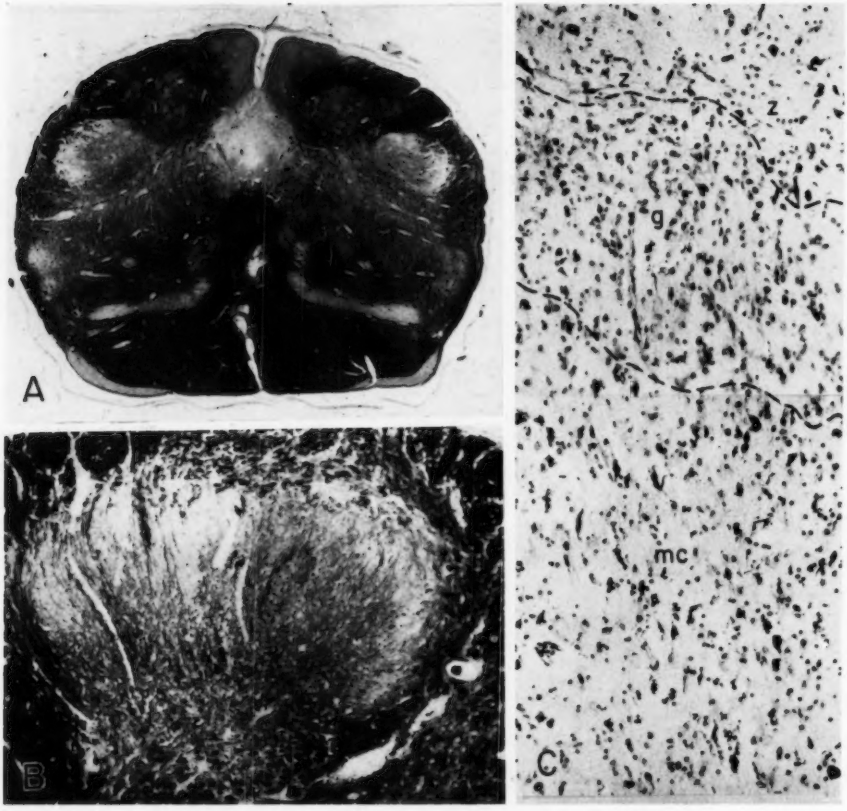

FIG. 7.—A, Cross section through the lower medulla. Heidenhain stain. B, Caudal spinal trigeminal nucleus. Heidenhain stain. C, Caudal spinal trigeminal nucleus. (*z*) Subnucleus zonalis; (*g*) Subnucleus gelatinosus; (*mc*) Subnucleus magnocellularis. Nissl stain.

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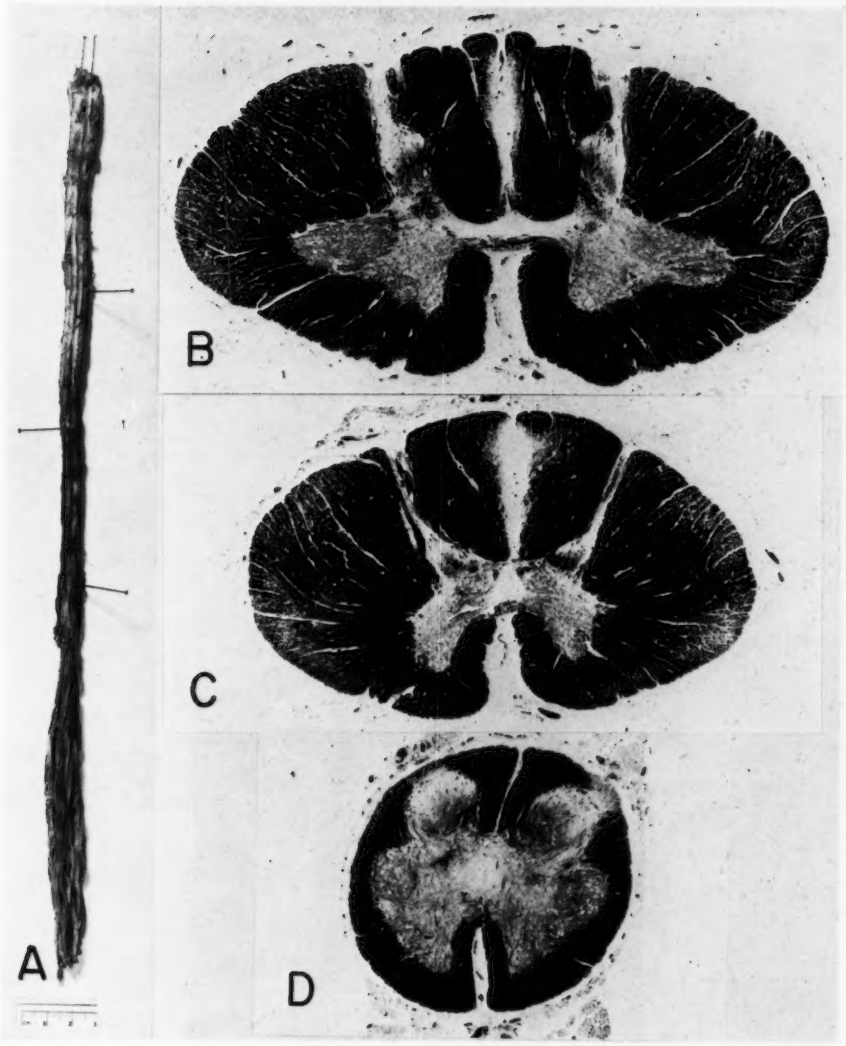

FIG. 8.—A, Ventral view of the spinal cord. B, Spinal cord, cervical level. Heidenhain stain. C, Spinal cord, thoracic level. Heidenhain stain. D, Spinal cord, sacral level. Heidenhain stain.

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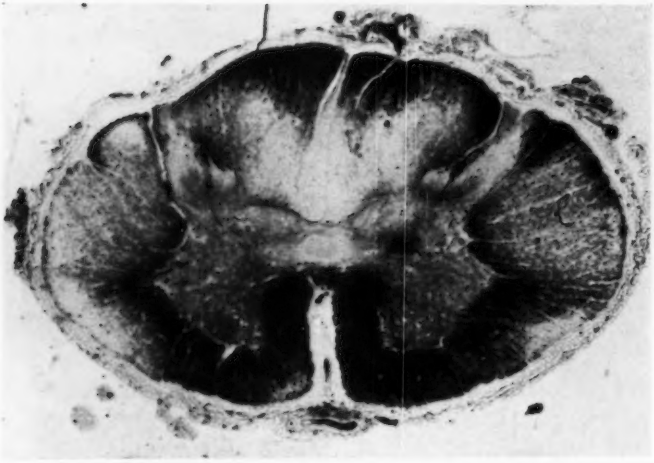

FIG. 9.—Spinal cord, upper lumbar level. Heidenhain stain.

FIG. 10.—Entry zone of dorsal root. Medial (X) heavily myelinated and lateral (XX) finely myelinated portion. Heidenhain stain.

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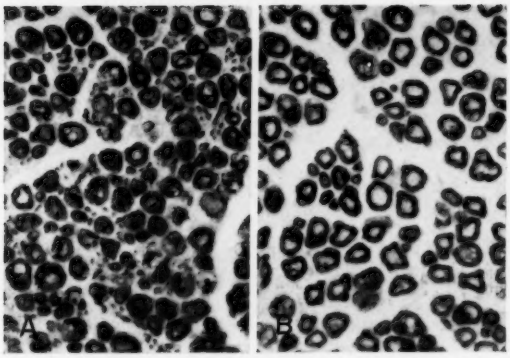

FIG. 11.—A, Cross section through a dorsal root, and B, cross section of a ventral root. Osmic acid stain. ×640.

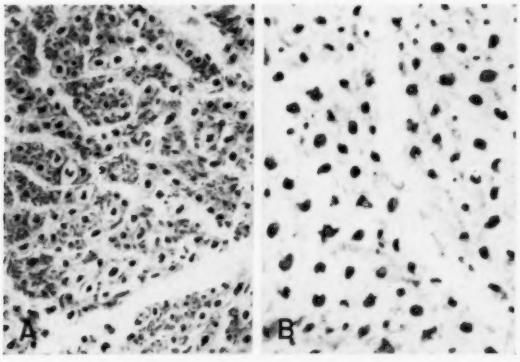

FIG. 12.—A, Cross section through a dorsal root and B, cross section through a ventral root. Schmidt's silver stain for axon cylinders. ×640.

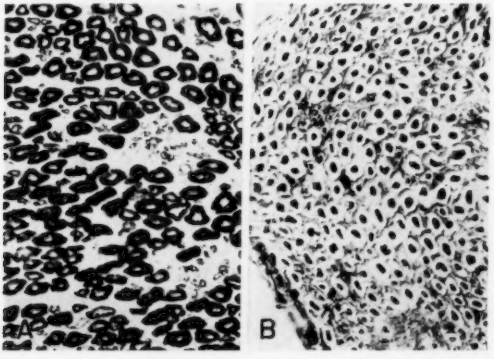

FIG. 13.—Brachial plexus. Cross section. A, Osmic acid stain and B, Schmidt silver stain for axon cylinders. ×640.

To illustrate article by D. W. Baxter and J. Olszewski.

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strate any gross abnormalities of those nervous system structures thought to be concerned with pain impulses. The possibility that the defect is actually an anatomical one, but in terms of organization rather than structure, is not excluded. The fact that the syndrome might result from perceptual or psychological variations is also discussed.

Acknowledgments

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AN ELECTROMYOGRAPHIC STUDY OF THE NOCICEPTIVE REFLEXES OF THE LOWER LIMB. MECHANISM OF THE PLANTAR RESPONSES[1]

BY

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INTRODUCTION

IN normal individuals stimulation of the sole of the foot produces plantar flexion of the great toe and flexion and adduction of the other toes. This is the normal plantar response (Wernicke, 1881). It is accompanied by dorsiflexion of the foot and flexion at the knee and hip (Babinski, 1898; Collier, 1899). Davidson (1931) and Morgenthaler (1948) obtained a great variety of reflex patterns with mechanical stimulation of the sole. In view of the danger of evoking quasi-voluntary movements or startle reactions with stimuli that are painful, the results of purely clinical studies are, however, difficult of interpretation.

It is generally accepted that the flexion reflex represents the mechanism for withdrawing an extremity from injury. Collier (1899) considered that flexion of the toes renders the sole of the foot lax, so that a sharp object penetrates less readily. It has been maintained that the normal plantar response is a part of the general flexion-reflex of the lower limb (Pedersen, 1954, and others). Plantar flexion of the toes, however, is in reality physiological extension. Babinski (1922) interpreted the normal plantar reflex as an atavistic grasp reflex, in contrast to the flexion reflex of the leg, which he considered to be a primitive defence reaction. Davidson (1931) states that no theory has adequately explained the plantar reflex.

In disorders of suprasegmental (pyramidal) function the normal plantar reflex is replaced by the Babinski reflex (Babinski, 1896, 1898; Fulton and Keller, 1932; and others), i.e. dorsiflexion of the great toe, often with dorsiflexion and fanning of the other toes. This, again, is commonly associated with flexion at the ankle, knee and hip. Electromyographic studies have shown that these reflexes have two components, an early

[1]Acknowledgment: This investigation was facilitated by a grant from the Swedish Medical Research Council.

response to stimulation of A fibres and a later more tonic response to C fibres in the afferent reflex arc (Kugelberg, 1948).

The view has been expressed that the Babinski plantar response is an integral part of a general flexion-reflex in man, homologous with the nociceptive flexion-reflex (Sherrington, 1910) of the spinal and decerebrate animal (Walshe, 1914, 1956). Marie and Foix (1912) and Walshe (1914) specified the differences between the normal and pathological plantar responses. They consider that the normal plantar response is a segmental reflex, akin to the cutaneous abdominal reflexes, involving no co-ordination, i.e. no reciprocal inhibition. It is abolished in lesions of the pyramidal tract and replaced by a new reflex which is not purely cutaneous and is a co-ordinated flexion movement of the whole limb. Thus, fundamentally the pathological plantar reflex should differ from the normal plantar reflex.

It has been shown (Kugelberg and Hagbarth, 1958) that the cutaneous abdominal reflexes are accompanied by contraction of the abdominal muscles and reciprocal inhibition of the erector spinæ muscles. In fact, it was found that the cutaneous abdominal reflexes are but one manifestation of an intricate mechanism for protection of the trunk where each skin area is functionally associated with the appropriate withdrawal muscles. These observations led to the present electromyographic study of the reflex patterns obtained by painful stimulation of various areas of the foot and buttock. The results elucidate the form and nature of the plantar responses and other cutaneous reflexes used in clinical studies.

Some of our results have been briefly reported elsewhere (Eklund, Grimby and Kugelberg, 1959).

Material and Methods

The experiments were performed on 25 normal individuals and 5 patients with paraparesis who exhibited the "pathological" flexion-reflex and the Babinski sign. In addition they were repeatedly performed on two of the authors (L. G. and E. K.).

In a majority of experiments the subjects lay in the recumbent position. In a few experiments they sat or stood.

Electric stimuli were delivered either to the skin or deep tissues of the foot. The cutaneous stimuli were delivered through three pairs of needle electrodes, 4 mm. apart, fixed in a rubber holder and pressed firmly against the skin. Stimulation of deep tissues was done with two needle electrodes, insulated except for the tip, inserted a few millimetres apart. A Grass stimulator, controlled by a master oscillator, provided square wave pulses of 1·5 msec. duration and a frequency of 500 per second, synchronized with the sweep of the cathode ray. The maximum strength of the current was 20 mA. In a majority of experiments the stimulus consisted of a series of shocks delivered over a period of 30 to 40 msec.

The reflex responses were recorded with bipolar or concentric needle electrodes. The position of the recording electrodes could be checked by stimulating the muscle through the recording needle and observing the movement elicited. The recordings were made with one, usually two condenser-coupled amplifiers connected to a double-beam cathode ray oscillograph and loudspeaker.

Results

The stimuli were definitely noxious and experienced like the thrust of a needle into the skin. In fact, the skin was often damaged at the site of stimulation. The stronger and more painful the stimulus the larger was the reflex response. Non-painful stimuli seldom evoked a reflex. The responses evoked in this investigation are regarded as nociceptive reflexes. The reflex activity was studied chiefly in muscles whose main function is flexion or extension.

In this paper physiological flexion is used to denote a movement which approximates the limb to the trunk and the reflex which produces this movement is called a flexion reflex. Thus dorsiflexion of the toes and foot is referred to here as flexion. Physiological extension is used to denote a movement which elongates the limb and the reflex which produces this movement is called an extension reflex. Table I shows the reflex patterns elicited by stimulation of different skin areas of the foot and buttock.

TABLE I

Site of Stimulus	*Reflex-movement*				
Normal subjects	*Toes*	*Ankle*	*Knee*	*Hip*	*Trunk*
Ball of toes	Flexion	Flexion	Flexion	Flexion	Flexion
Ball and hollow of foot ..	Extension	Flexion	Flexion	Flexion	Flexion
Plantar surface of heel ..	Extension	Extension	Flexion	Flexion	Flexion
Buttock	Extension	Extension	Flexion	Extension	Extension
Pathological conditions					
Ball of toes, ball and hollow of foot, heel	Flexion	Flexion	Flexion	Flexion	Flexion

Normal Responses to Stimulation of the Foot

Stimulation of the ball and hollow of the foot.—The muscles engaged are listed in Table II. Stimuli to the ball or hollow of the foot elicited a reflex movement consisting of plantar flexion of the toes and flexion at the ankle, knee and hip. A reflex response was recorded in the flexor hallucis brevis after a latency of 70 to 80 msec. (fig. 1 Aa). This latency is shorter than when the response is evoked by clinical modes of stimulation (Magladery *et al.*, 1958). A stimulus applied during sustained voluntary dorsiflexion of the toes evoked a reflex response in the flexor hallucis brevis with reciprocal inhibition of the extensor hallucis brevis (fig. 1 Ab, Plate LX). Simultaneously a reflex discharge was observed in the interossei and the abductor of the fifth toe. This results in the normal plantar response elicited by clinical methods.

A reflex response was recorded in the extensor hallucis longus (fig. 2 Aa) and extensor digitorum longus. Thus the long flexors of the toes did not appear to take part in the plantar flexion of the toes. One would expect that in patients with paralysis of the short flexors of the toes contraction

of the long extensors would dorsiflex the toes, at least when the ankle is not free to flex. That this would seem to be the case is shown by reports of a false Babinski sign in patients with paralysis of the short flexors (Monrad-Krohn and Lossius, 1921; among others).

A reflex response was recorded in the anterior tibial muscle with reciprocal inhibition of the gastrocnemius (fig. 2 A, b and c) and in the long extensors of the toes with reciprocal inhibition of the long flexors, resulting in dorsiflexion of the foot. The reflex response had a minimal latency of 55 msec. With an estimated conduction velocity of 40 m.p.s. in the afferent reflex arc and 55 m.p.s. in the efferent arc, the central delay is 4 msec. This shows that the reflex is a spinal multisynaptic reflex, which is in good agreement with the conclusion of Pedersen (1954).

A reflex response was recorded in the inner hamstring muscles, among others, with reciprocal inhibition of the vastus internus and externus (fig. 3 a and b), producing flexion at the knee. Flexion at the hip is produced by contraction of the tensor fasciæ latæ (fig. 3 c), among other muscles, and reciprocal inhibition of the greater part of the gluteal muscles. The rectus femoris, which extends over two joints and functions both as a flexor of the thigh and extensor of the lower leg, acts here as a flexor.

The reflex may also spread to the abdominal wall, with contraction of the rectus abdominis (fig. 3 d) and reciprocal inhibition of the erector spinæ muscles. This response has a short latency which indicates that the activity spreads rapidly within the spinal segments taking part in the reflex.

The reflex response in one muscle is frequently followed by a rebound in the antagonist (fig. 3 a).

Stimuli to the deep tissues of the sole evoked a reflex response in the flexor hallucis brevis (fig. 1 Ac) with reciprocal inhibition of the extensor hallucis brevis. This was accompanied by flexion at the ankle, knee and hip.

Thus, the normal plantar reflex is a co-ordinated movement consisting of plantar flexion (physiological extension) of the toes and flexion at the ankle, knee and hip and sometimes of the trunk (Table I).

Stimulation of the ball of the toes.—The muscles engaged are listed in Table II. *Stimuli to the toes produced dorsiflexion (physiological flexion) of the toes. This is the reverse to that obtained with stimulation of the ball of the foot.* The reflex pattern at the ankle, knee, hip and trunk, however, remained unchanged. The electromyograms (20 subjects) showed a reflex response in the extensor hallucis brevis (fig. 1 Ba) with reciprocal inhibition of the flexor hallucis brevis (fig. 1 Bb), and in the extensor hallucis longus with reciprocal inhibition of the flexor hallucis longus.

Stimuli to the ball of the great toe evoked a strong reflex response in the hallux and a weaker response in the lesser toes. Conversely, a stimulus

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applied to the ball of the lesser toes evoked a strong response in the lesser toes and a weaker response in the great toe. Pricking or stroking the ball of the toes with a pin will also evoke dorsiflexion of the toes. Unless the stimulus is very weak, however, there is a danger that the toes will be passively dorsiflexed. Consequently it is somewhat difficult to observe the reflex clinically except in subjects with a low reflex threshold.

Stimuli into the ball of the hallux evoked the general flexion-reflex, including dorsiflexion of the hallux (fig. 1 Bc).

Thus, stimuli to the surface or deep tissues of the ball of the toes evoke a co-ordinated reflex movement consisting of dorsiflexion of the foot and toes and flexion at the knee, hip and trunk (Table I and fig. 10).

Stimulation of the plantar surface of the heel.—Stimuli applied to the plantar surface of the heel produced plantar flexion of the toes and foot and flexion at the knee and hip. This response is the same as that obtained with stimulation of the ball and hollow of the foot, except as regards the ankle, where it is reversed. The electromyograms showed a reflex response in the gastrocnemius with reciprocal inhibition of the anterior tibial muscle (fig. 2 B a, b, c).

Stimulation of the dorsum of the foot.—The reflex threshold is considerably higher on the dorsum of the foot than on the sole. Moderately strong stimuli to the dorsum of the foot evoked a reflex response in the inner hamstring muscles and reciprocal inhibition of the quadriceps (fig. 4 c), resulting in flexion at the knee. This was the response most readily obtained. Stronger stimuli produced, in some subjects, a response in the gastrocnemius (fig. 4 a) and reciprocal inhibition of the anterior tibial muscle, resulting in plantar flexion (physiological extension) at the ankle. Weak plantar flexion of the toes and flexion at the hip was also observed (fig. 4 d).

Although the maximal stimulus strength of our stimulator failed to evoke a reflex response in the gastrocnemius in some of our subjects, the response obtained in others suggests that the skin on the dorsum of the foot is functionally associated predominantly with an extension reflex (plantar flexion) at the ankle. If this theory is correct, concurrent stimulation of the dorsum and, for example, the ball of the foot would result in competition between the two opposing reflexes. That this is what actually occurs is shown in fig. 5, from a subject with no overt extension reflex. A stimulus to the ball of the foot evoked a moderately strong reflex in the anterior tibial muscle (fig. 5 a). Simultaneous stimulation of the ball and dorsum of the foot abolished this reflex (fig. 5 b). Evidently a clash occurred between the two reflexes.

Thus, stimulation of the dorsum of the foot evoked weak plantar flexion (physiological extension) of the toes and foot, stronger flexion at the knee and weak flexion at the hip. Although the reflex pattern in the limb was the same as that obtained with stimulation of the plantar surface

of the heel, the relative strength of the reflexes differed at the different joints. The reflex response was strongest at the knee with stimulation of the dorsum of the foot while the responses at the ankle, knee and hip were approximately the same with stimulation of the heel.

Lability of reflex responses.—Stimulation of the ball of the toes invariably produced dorsiflexion (physiological flexion) of the toes and foot. Stimulation of the ball, hollow, heel or dorsum of the foot showed some variability of the reflex pattern. A change in the intensity or duration of the stimulus or mere repetition of the stimulus was sometimes sufficient to diminish or abolish an extension (plantar flexion) response and elicit or increase a flexion (dorsiflexion) response.

It is not clear which stimulus parameter favours the one or the other of the reactions. Reflex reversal, when it occurred, was somewhat unpredictable, but it would seem that very strong stimuli favour the flexion-reflex at the expense of the extension-reflex.

This is illustrated in fig. 6. A stimulus to the hollow of the foot evoked a reflex response in the flexor hallucis brevis (a) with plantar flexion of the toes. An increase in the intensity and duration of the stimulus now evoked, at a shorter latency, a strong response in the extensor hallucis brevis and a weaker response in the flexor hallucis brevis (b). Reflex reversal with complete inhibition of activity in the short flexors of the toes has been observed, but is less common.

In the subject illustrated in fig. 7, a strong stimulus to the ball of the foot evoked a weak reflex response in the extensor hallucis brevis (a) with dorsiflexion of the toes. A strong stimulus during voluntary dorsiflexion of the toes evoked a strong reflex response in the flexor hallucis brevis and reciprocal inhibition of the extensor hallucis brevis (b), i.e. reversal of the reflex response.

Reversal is considered germane to concealed reflexes (Creed *et al.*, 1932). The receptive fields of the extension and flexion reflexes apparently overlap, but one reflex dominates and the other is concealed.

Inhibition.—Various kinds of inhibition were observed. Some of them have been described in an earlier study on the abdominal skin reflexes (Kugelberg and Hagbarth, 1958) and will be only briefly mentioned here.

A reflex evoked in a muscle under voluntary contraction was found to have an inhibitory effect on the voluntary activity for a period following the reflex response (fig. 8 b and c). This period of inhibition is probably identical with the silent period following a tendon-jerk, described first by Hoffmann (1920).

Further, inhibition of voluntary activity frequently occurred 5 to 10 msec. before the reflex response (fig. 8 b–d). Consequently it cannot be secondary to the reflex response. The reflex threshold was not sufficiently stable to permit accurate determination of the excitability changes with double shock stimulation and it is therefore not clear whether this type of

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inhibition is independent of volition. If this is the case, it may be the result of stimulation of inhibitory afferents since in most skin fields there is an overlap of the excitatory and inhibitory elements.

Reciprocal inhibition has been mentioned earlier. Hoffmann, Schenck and Tönnies (1948) observed inhibition of voluntary activity in the gastrocnemius and soleus muscles following an electric shock to the skin of the foot. This was also observed by Dodt and Koehler (1950) following stimulation of locally anæsthetized skin which they interpreted as deep stimulation. These authors regarded this as reciprocal inhibition, although they did not observe a reflex contraction in the antagonistic muscle. They consider that reciprocal inhibition is a more sensitive index of a reflex than the reflex response itself. Schenck and Koehler (1949) observed concomitant inhibition of voluntary activity in the gastrocnemius and anterior tibial muscles following an electric shock to the foot.

We have also observed such "ambivalent" inhibition. It was obtained most easily with stimulation of areas with a high reflex threshold, e.g. the dorsum of the foot (fig. 4 b). That a joint is free to move during a withdrawal movement may have some functional significance.

Crossed reflexes.—Stimulation of the sole of the foot evoked a reflex response in the contralateral leg. The response was strongest in the proximal muscles, e.g. the tensor fasciæ, quadriceps and hamstring muscles. The latency of the response in the contralateral quadriceps was the same as that in the ipsilateral anterior tibial muscle. This shows that the crossed reflex is a spinal reflex and not a startle reaction or voluntary contraction. The crossed reflex response occurred almost synchronously in the extensors and flexors of the knee (fig. 3 e). This results in a stiffening of the contralateral leg during the general flexion-reflex in the ipsilateral leg. The crossed reflex probably represents a mechanism for maintenance of posture.

Stimulation of the Buttock

A stimulus to the buttock when the subject was in the upright position evoked a reflex response in the erector spinæ, gluteal, hamstring, gastrocnemius and flexor digitorum brevis muscles with reciprocal inhibition of their antagonists. The responses were strongest in the erector spinæ and gluteal muscles and weakest in the distal muscles.

The resulting movement is strong extension of the lower part of the trunk and hip, moderate flexion at the knee, weak extension at the ankle and plantar flexion of the toes (Table I). This movement withdraws the buttock from the stimulus (fig. 10).

The reflex response in the knee flexors was followed by a strong reflex rebound in the extensors. The reflex rebound apparently acts as a brake on the flexion movement at the knee and helps to maintain balance.

The withdrawal movement includes flexion at the knee. A stimulus to the buttock when the subject is in the sitting position produces, again,

flexion at the knee. Extension at the knee would have been the appropriate defence reaction. It seems as though the reaction is designed primarily for defence of the buttock when the subject is in the upright position.

Crossed reflex.—The reflex response in the ipsilateral limb was accompanied by a similar response in the contralateral limb, but of lesser intensity. A stimulus applied nearer the midline increased the strength of the crossed reflex resulting in greater symmetry of the two sides.

Stimulation of the anterior proximal part of the thigh.—This produced extension at the knee and ankle and plantar flexion of the toes.

Pathological Responses to Stimulation of the Foot

The reflex responses to stimulation of the foot were studied in 5 patients with paraparesis. Since voluntary contraction was impaired in these patients no systematic attempt was made to study inhibition in the antagonistic muscles. The muscles engaged in the reflex (Table II) are in

TABLE II

	Normal subjects		*Pathological conditions*
Muscles	*Stimulation of the ball and hollow of the foot*	*Stimulation of the ball of the toes*	*Stimulation of the ball and hollow of the foot*
Extensor digitorum brevis	—	+	+
Extensor hallucis brevis	—	+	+
Interossei (part)	+	+	+
Flexor digitorum brevis	+	—	—
Flexor hallucis brevis	+	—	—
Extensor digitorum longus	+	+	+
Extensor hallucis longus	+	+	+
Tibialis anterior	+	+	+
Fibularis longus	+	+	+
Flexor digitorum longus	—	—	
Flexor hallucis longus	—	—	
Gastrocnemius	—	—	
Soleus	—	—	
Semimembranaceus (part)	+	+	+
Semitendineus (part)	+	+	+
Biceps femoris (part)	+	+	+
Sartorius	+	+	+
Rectus femoris	+	+	+
Vastus tibialis et fibularis femoris	—	—	
Adductores femoris (part)	+	+	+
Tensor fasciæ latæ	+	+	+
Glutei (larger part)	—	—	
Rectus and obl. abdominis	+	+	+
Erector spinæ	—	—	

+ denotes muscles contracting. — denotes muscles inhibited.

good agreement with the findings of Walshe (1914). Our observations confirm his view that the Babinski reflex is an integral part of the general flexion-reflex of the leg.

Stimulation of the ball and hollow of the foot evoked the same reflex response as that obtained in normal subjects with stimulation of the ball of the toes (Tables I and II), except in one patient in whom the response in the interossei differed. In both instances the electromyogram showed a reflex response in the extensor hallucis brevis and reciprocal inhibition of the flexor hallucis brevis (fig. 9 a), as well as a reflex discharge in the extensor hallucis longus and reciprocal inhibition of the flexor hallucis longus. The latency of the response was the same in both instances, which is in agreement with the observations of Pedersen (1954) on other leg muscles.

Not only the plantar flexion of the great toe but also the plantar flexion of the foot normally obtained with stimulation of the heel and dorsum of the foot was reversed (fig. 9 c and d). Thus the extension reflex (plantar flexion) normally present in the toes and foot was abolished and replaced by a flexion reflex (dorsiflexion) (Table I).

Conclusions

Normal responses.—The normal nociceptive reflexes of the lower limb are co-ordinated movements in which most, if not all, of the muscles of the leg take part. They represent a much more elaborate mechanism of defence than is generally realized. Each skin area is associated with a specific reflex pattern (Table I).

The main function of the nociceptive reflexes of the foot is defence of the sole when the subject is in the upright position, e.g. during walking, running or jumping. There is little doubt that from this point of view the various reflexes elicited from the foot and described here are specifically adapted to the form of the human foot and represent the adequate withdrawal movement in relation to the site of stimulation.

The ball of the toes is the only area for which flexion at all leg joints is the adequate protection movement. Indeed, noxious stimuli to the ball of the toes regularly elicited the general flexion-reflex, including dorsiflexion of the great toe (fig. 10).

Stimuli applied to the ball and hollow of the foot evoke the normal plantar reflex, i.e. plantar flexion (physiological extension) of the toes and flexion at the ankle, knee and hip. This is the adequate movement for protection of this area. When the subject is in the upright position plantar flexion of the toes raises the sole from the ground and so long as the toes are in contact with the ground assists in the general withdrawal movement.

Extension (plantar flexion) of the foot and toes is the adequate movement for protection of the heel. This, combined with flexion at the knee and hip, raises the heel from the ground. Indeed, this is the reflex pattern

evoked by stimulation of the heel. The flexion of the trunk observed is a natural adjunct of a general flexion-reflex of the leg.

The organization of the reflex elicited from the dorsum of the foot is essentially the same as that of the reflex elicited from the sole. The reflex threshold, however, is considerably higher and the relation between withdrawal movement and site of stimulation is possibly less refined. Noxious stimuli to the dorsum of the foot evoke a strong flexion-reflex at the knee and sometimes a weaker extension-reflex at the ankle, resulting in withdrawal of the foot backwards.

Stimulation of the buttocks likewise elicits the appropriate withdrawal movement for defence of the buttock when the subject is in the upright position (fig. 10).

Thus, the functional organization of the nociceptive reflexes of the leg is such that an appropriate withdrawal movement ensues, regardless of the locus of the stimulus. This is obtained by the integration of flexion and extension reflexes. There is certainly nothing "primitive" about such a highly purposeful reflex system.

The flexion-reflex evoked by stimulation of the foot has a widespread distribution. This is the result of the functional organization of the reflex, since flexion at joints most coincides with the adequate withdrawal movement for protection of the foot. The reflex extension of the leg evoked by stimulation of the foot is much more local. Stimuli to the buttock and anterior proximal part of the thigh evoke, for the same reason, widespread extension while the reflex-flexion is more local (Table I).

It is evident that reflex-extension often results in withdrawal from the stimulus. It is not, however, clear whether this is its sole function. For instance, the reflex responses evoked by a stimulus to the buttock are strong in the proximal muscles and very weak in the distal muscles. The weak extension movements of the foot and toes probably add little to the speed and magnitude of the main withdrawal movements occurring proximally. They do, however, elongate the limb and keep the foot and toes on the ground despite the flexion at the knee. This certainly helps to maintain posture. The strong reflex rebound in the quadriceps observed after the reflex response in the knee flexors and the crossed reflex elicited from the sole of the foot apparently serve the same purpose.

The question may arise whether the adequate defence reactions consist of several flexion and extension reflexes or of one widespread flexion or extension reflex mechanism with highly variable local signs. It is probably only a question of nomenclature.

The defence reactions of the leg are organized on a functional basis, not on an anatomical. The responses are multisegmental reflexes so far as stimuli well above reflex threshold are concerned. Furthermore, a stimulus applied for instance to the ball of the foot evokes plantar flexion of the toes while a stimulus a few millimetres away on the ball of the toes produces

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dorsiflexion. The two skin points may be so chosen that they are innervated by the same spinal segment and the same cutaneous nerve, yet the responses are the reverse. One may ask how such remarkable functional precision is accomplished. These reactions may, of course, be innate, although it is difficult to understand how this is possible when one considers how closely they are associated with function and how little dependent on anatomical factors. There is a possibility that at least the finer adjustment of the reflex is the result of experience and training during early life (cf. Hagbarth and Kugelberg, 1958).

Nociceptive reflexes similar to those observed in the lower limb and trunk occur in other parts of the body. The cutaneous reflexes of the sternomastoideus, trapezius, latissimus dorsi and pectoralis muscles described by Duensing (1940) are examples. Certain facial reflexes belong to this group (Kugelberg, 1952; Ekbom, Jernelius and Kugelberg, 1952) and defence reflexes similar to those in the leg have been observed by us in the upper limb. A sufficiently strong nociceptive stimulus will probably produce such reactions anywhere on the body. The threshold of the nociceptive reflexes, however, varies considerably in different regions since the threshold must accord with the biological function of the reflex. Only in certain regions is the threshold sufficiently low to permit the use of the reflex in clinical studies without too much discomfort to the patient.

The "pathological" flexion reflex and the Babinski sign.—The receptive fields of the flexion and extension reflexes overlap and the maintenance of balance between the two is strongly dependent on cerebral control. In disorders of suprasegmental function the balance is impaired. The receptive field of the nociceptive extension reflex is greatly diminished or abolished and a flexion reflex dominates (Table I).

The "pathological" flexion reflex, including the Babinski sign, has been regarded as a new reflex not present in the normal state. There is, however, little essential difference between the normal and the "pathological" flexion reflexes. The normal flexion-reflex evoked by stimulation of the ball of the toes consists of contraction of all limb flexors and dorsiflexors of the foot and toes and reciprocal inhibition of their antagonists. It is evoked by noxious stimuli to the skin or deep tissues. The same definition can be applied to the "pathological" flexion reflex. The muscles engaged in both reflexes are the same (Table II). Reflex rebound and a crossed reflex accompany both. In both the reflex spreads to the abdominal wall. The main difference lies in the size of the receptive field and the duration of the reflex contraction. These differences are quantitative rather than qualitative. Lack of inhibition of the normal flexion-reflex and diminished competition from the extension-reflex may explain the largeness of the receptive field of the "pathological" flexion-reflex. Increased excitability of the reflex centre explains the more tonic

appearance of the "pathological" flexion-reflex, since the central reflex pathway is then more open to discharges in the afferent reflex arc (Kugelberg, 1948).

The conclusion must therefore be drawn that the "pathological" flexion-reflex, including the dorsi-flexion of the hallux, and the normal flexion-reflex are identical. In fact, it would be remarkable if this were not so, since it would mean that the organism, instead of using a powerful reflex system already present in the spinal cord, invents a new one to do exactly the same job, namely, flex the limb in a co-ordinated movement.

It is, however, clear that the crude flexion reflex, as displayed, for example, in cases with complete division of the spinal cord, must be modified if it is to fulfill its function of protecting the foot in the intact organism. The reflex threshold must be raised and more strictly attuned to nociceptive stimuli in order not to interfere with the normal function of the leg. If an individual with an uncontrolled flexion reflex were to try to walk he would soon fall to the ground in flexor spasms. Furthermore, the receptive field must be diminished, since an extension reflex must take part in the defence reaction in order to extend the joints where necessary. In other words, the spinal nociceptive flexion and extension reflexes must be integrated in a defence mechanism with discriminating capacity as regards the strength, modality and site of the sensory stimulus. This refinement is only obtained by the co-operation of supraspinal centres.

From this point of view it is clear why the ball of the toes is the only area from which the flexion-reflex of the entire limb can be evoked normally. This is because a general flexion of the leg coincides here with the adequate withdrawal movement. In our opinion, dorsiflexion of the great toe in this movement is identical with the dorsiflexion of the great toe in the Babinski sign. *What is pathological about the Babinski sign is not the upgoing hallux as such, but the fact that it is elicited from a receptive field in which an extension reflex (plantar flexion) is normally dominant. The Babinski sign is the result of encroachment of the receptive field of the normal flexion reflex upon that of the normal extension reflex.*

Theoretically, dorsiflexion of the foot following stimulation of the heel has the same significance as the Babinski response. In fact, this applies to reversal of the normal extension reflex to flexion in any of the joints of the leg (Table I). Reflex reversal produced by stimuli to areas other than the sole of the foot, however, is a less sensitive index of abnormality since the more proximal the site of stimulation the higher is the threshold of the flexion-reflex.

A Babinski sign resulting from imbalance between the extension and flexion reflexes would explain some features of the response that have been debated. When it was accepted that dorsiflexion of the great toe is an integral part of the general flexion-reflex of the leg, the question arose how the two can vary independently of each other. Strong dorsi-

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flexion of the hallux may be accompanied by weak flexion of the leg or vice versa. This, however, is only to be expected, since dorsiflexion of the toes is dependent on a variable which does not affect flexion at the other joints. The dorsiflexion of the toes is counteracted by the normal plantar reflex while the flexion at the ankle, knee and hip is shared by both the normal and the "pathological" reflexes (Tables I and II).

The optimal area for eliciting the Babinski sign is the lateral part of the sole. This is explained by the fact that competition from the normal plantar response is less here than on the mesial part of the sole which is the optimal area for eliciting plantar flexion of the great toe.

"*Pathological*" *extension reflexes.*—The various types of ipsilateral extension reflexes described in paraplegia and other pathological conditions (*see* Marshall, 1954) may be identified with the normal reflex pattern evoked by stimulation of various parts of the leg and buttock (Table I). Thus, the widespread normal extension-reflexes and the "pathological" extension-reflexes are most easily obtained from the proximal part of the limb and the buttock. The "pathological" extension reflexes are probably nothing but the normal extension responses out of order.

The normal extension-reflexes observed in man are somewhat difficult to compare with those found in the experimental animal. Ipsilateral extension-reflexes were observed in spinal animals by Sherrington and Sowton (1911), Graham Brown (1911, 1912) and Graham Brown and Sherrington (1912). The integration of normal flexion and extension reflexes into highly purposeful withdrawal movements has received little attention in the experimental animal. This is not surprising, however, since the integration, at least in man, is broken down in suprasegmental lesions.

Hagbarth (1952) found, in spinal and decerebrate cats, that the extensor muscles were inhibited from most parts of the limb but excited from a skin area mainly localized over the muscle itself while the flexor muscles were excited from most parts of the limb but inhibited from a skin area mainly localized over the antagonistic extensor muscle. Such a relationship between skin area and muscle contraction will often, but not always, result in an appropriate withdrawal movement. Too much emphasis should not, however, be laid on anatomical relations which apparently are the result, rather than the cause, of the organization of a mechanism based on function. The normal defence reactions are widespread movements rather than local contractions. This applies both to the flexion and the extension reflexes.

To sum up, the nociceptive reflexes of the leg are designed to force the body to escape from stimuli likely to damage it. This is performed with considerable precision. In disorders of suprasegmental control, however, this mechanism is impaired. The normal reflex thresholds are then

raised or lowered and the harmonious integration of the extension and flexion components is broken down.

Summary

The spinal nociceptive reflexes of the lower limb have been electromyographically studied in 27 normal individuals and 5 patients with paraparesis.

The reflexes were elicited by painful electric shock stimuli to the skin and deep tissues of (a) the balls of the toes, (b) the ball and hollow of the foot, (c) the plantar surface of the heel, (d) the dorsum of the foot and (e) the buttock. The distribution of reflex contractions and inhibitions in the lower limb and trunk was recorded.

I. Normal Conditions

(1) The nociceptive reflexes are co-ordinated movements which may involve the entire ipsilateral limb, at least the lower part of the trunk and the proximal part of the contralateral limb.

(2) The reflex patterns form the adequate movement for withdrawal from a stimulus. The mechanism is designed primarily to defend the limb when the subject is in the upright position with maintenance of posture.

(3) The withdrawal movement consists of the harmonious integration of flexion and extension reflexes, except with stimulation of the ball of the toes, when a general flexion-reflex of the limb, including dorsiflexion of the hallux, is evoked.

Stimulation of the foot evokes a widespread reflex-flexion and a more local reflex-extension. Stimulation of the buttock evokes a widespread reflex-extension and a more local reflex-flexion.

(4) The receptive fields of the flexion and extension reflexes show considerable overlapping. The reflex evoked by stimulation of a given area is generally the result of balance between two opposite reactions, one of which is dominant and the other is concealed.

(5) Inhibition of voluntary activity preceding the reflex response is described.

II. Pathological Conditions

(1) In disorders of suprasegmental (pyramidal) control the extension-reflex is diminished or abolished and a flexion-reflex dominates in a greater part of the receptive field.

(2) It is concluded that the "pathological" flexion-reflex is identical with the normal flexion-reflex evoked by stimulation of the ball of the toes. Both the "pathological" and the normal flexion-reflexes are nociceptive reflexes evoked from the skin or deep tissues of the foot. Both consist of contraction of all limb flexors and dorsiflexors of the foot and

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toes with reciprocal inhibition of their antagonists. The dorsiflexion of the great toe, which is an integral part of both, is thus of the same nature.

The Babinski sign is the result of encroachment of the receptive field of the normal flexion-reflex on that of the normal extension-reflex. Theoretically, reflex reversal from extension to flexion at any joint of the limb (here described in the ankle) has the same significance as the Babinski sign.

(3) An extension reflex evoked from the proximal part of the limb and a crossed reflex in normal subjects are described. These reflexes are probably of the same nature as the extension reflexes and the crossed reflexes observed, for example, in paraplegics.

(4) The "pathological" reflexes mentioned above are not new reflexes. They are the result of the break down of the harmonious integration of flexion and extension components in the normal reflex mechanism. Disorders of suprasegmental control impair the discriminating capacity of the reflex mechanism as regards the strength, modality and site of the sensory stimulus.

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WERNICKE, C. (1881) "Lehrbuch der Gehirnkrankheiten für Aerzte und Studirende." Kassel. Vol. 1.

LEGENDS FOR PLATES

PLATE LX

FIG. 1.—Responses from flexor hallucis brevis (upper tracings) and extensor hallucis brevis (lower tracings).

Column A: Stimulus to ball of the foot. a, Reflex discharge in flexor hallucis brevis. b, During contraction of extensor hallucis brevis, reciprocal inhibition of voluntary activity (4 superimposed responses). c, Deep stimulation: reflex discharge in flexor hallucis brevis.

Column B: Stimulus to ball of hallux. a, Reflex discharge in extensor hallucis brevis. b, During contraction of flexor hallucis brevis, reciprocal inhibition of voluntary activity (4 superimposed responses). c, Deep stimulation: reflex discharge in extensor hallucis brevis. Time, in this and the following figures: 10 msec.

FIG. 2.—Responses (except in Aa) from the anterior tibial (upper tracings) and gastrocnemius-soleus (lower tracings).

Column A: Stimulus to ball of the foot. a, Reflex discharge in extensor hallucis longus. b, Reflex discharge in anterior tibial. c, During voluntary contraction of gastrocnemius, reciprocal inhibition of voluntary activity (3 responses superimposed).

Column B: Stimulus to plantar surface of the heel. a, Reflex discharge in the gastrocnemius in two bursts with rebound in anterior tibial. b, As in *a*, from another subject, with no rebound in anterior tibial. c, During contraction of anterior tibial, inhibition of voluntary activity (5 response superimposed).

PLATE LXI

FIG. 3.—Stimulus to the ball of the foot. a, Reflex discharge in inner hamstring (upper tracing) with strong rebound in vastus internus (lower tracing). b, During contraction of vastus internus, reciprocal inhibition of voluntary activity (4 responses superimposed). c, Reflex discharge in tensor fasciæ latæ. d, Reflex discharge in lower part of the rectus abdominis (lower tracing) at a shorter latency than the response in the anterior tibial (upper tracing). e, Crossed reflex response in the contralateral inner hamstring (upper tracing) and vastus internus (lower tracing).

FIG. 4.—Stimulus to dorsum of the foot. a, Reflex discharge in the gastrocnemius (lower tracing) with weak rebound in the anterior tibial (upper tracing). b, In another subject, during concomitant contraction of both muscles, showing "ambivalent" inhibition. c, Reflex discharge in the inner hamstring (upper tracing) with reciprocal inhibition in the vastus internus (lower tracing). d, Weak reflex discharge in the tensor fasciæ latæ.

FIG. 5.—Stimulus to the ball of the foot evoked a reflex discharge in the anterior tibial (a). Stimuli applied simultaneously to the ball and dorsum of the foot inhibited the reflex (b).

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PLATE LXII

FIG. 6.—Showing lability of responses. Stimulus to the ball of the foot. Upper tracings from flexor hallucis brevis. Lower tracings from extensor hallucis brevis. a, Reflex discharge only in the flexor hallucis brevis. b, An increase in the intensity and duration of the stimulus evoked, at a shorter latency, a strong reflex discharge in the extensor hallucis brevis and a weaker discharge in the flexor hallucis brevis.

FIG. 7.—Stimulus to the ball of the foot. Responses from flexor hallucis brevis (upper tracings) and extensor hallucis brevis (lower tracings). a, During relaxation, weak reflex discharge in extensor hallucis brevis, none in flexor hallucis brevis. b, During contraction of extensor hallucis brevis, reversal of response; reflex discharge in flexor hallucis brevis with reciprocal inhibition in extensor hallucis brevis.

FIG. 8.—Inhibitory phenomenon. Stimulus to the ball of the foot. Responses from anterior tibial muscle. a, During relaxation. b, During strong voluntary contraction of anterior tibial, showing reflex response preceded and followed by inhibition of voluntary activity. c, as in b (5 superimposed responses). d, as in b, but at higher sweep speed (time: 2 msec.).

FIG. 9.—From patient with paraparesis. a, Stimulus to the ball of the foot evoked a reflex discharge in the extensor hallucis brevis (lower tracing) and reciprocal inhibition in the flexor hallucis brevis (upper tracing). b, Stimulus to the ball of the hallux evoked a reflex discharge in the extensor hallucis brevis (upper tracing) and anterior tibial (lower tracing). c, Stimulus to the plantar surface of the heel, and d, dorsum of the foot evoked the same responses as in (b).

PLATE LXIII

FIG. 10.—Schematic drawing of the reflex pattern of movement obtained by stimulation of the ball of the great toe (left) and buttock (right). The filled in areas denote the trunk muscles involved.

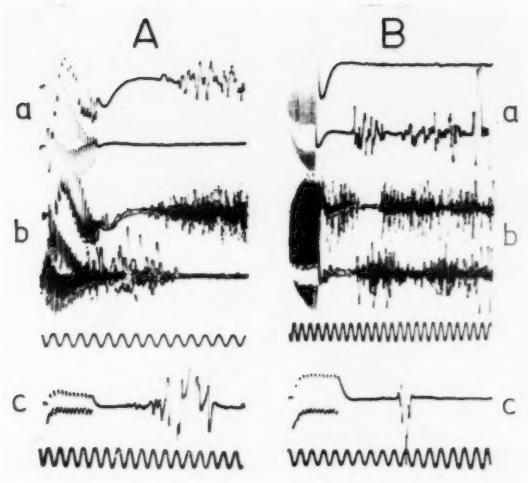

FIG. 1.

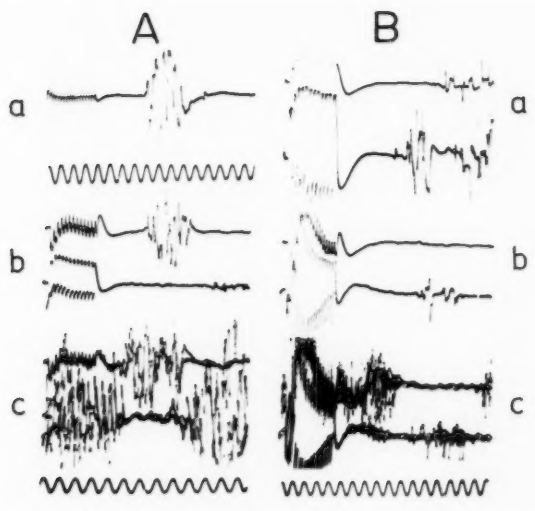

FIG. 2.

To illustrate article by Eric Kugelberg, Kerstin Eklund and Lennart Grimby.

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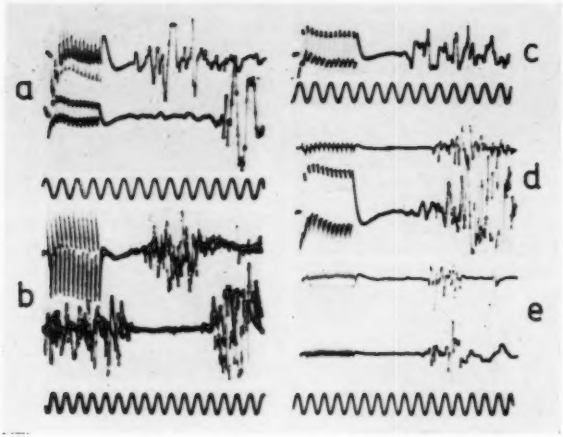

FIG. 3.

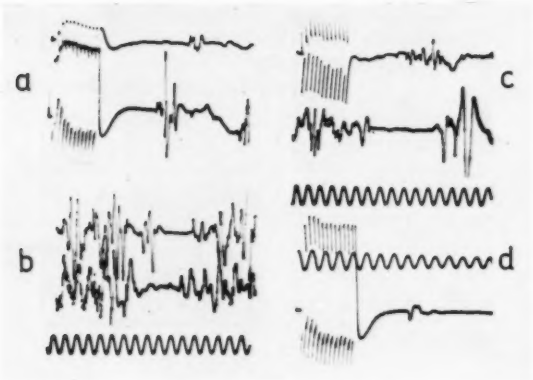

FIG. 4.

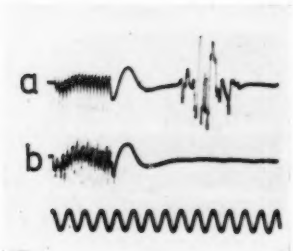

FIG. 5.

To illustrate article by Eric Kugelberg, Kerstin Eklund and Lennart Grimby.

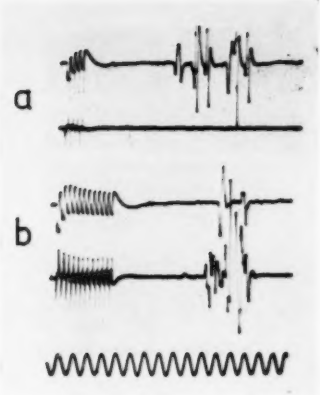

FIG. 6.

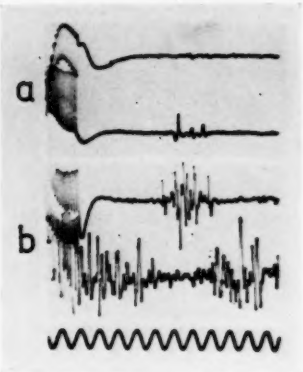

FIG. 7.

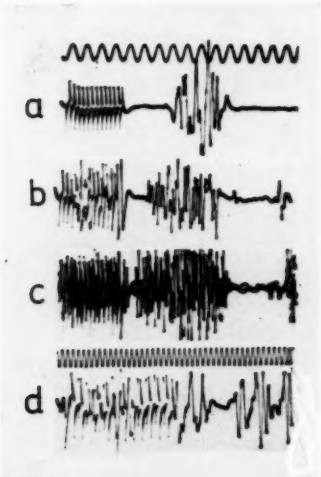

FIG. 8.

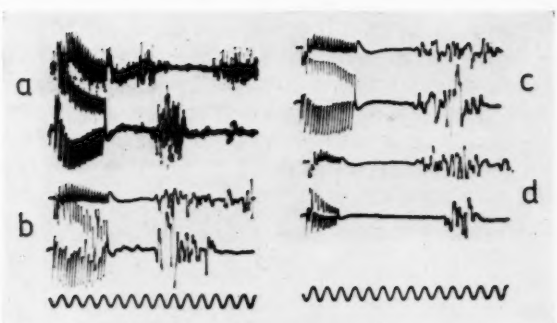

FIG. 9.

To illustrate article by Eric Kugelberg, Kerstin Eklund and Lennart Grimby.

FIG. 10.

To illustrate article by Eric Kugelberg, Kerstin Eklund and Lennart Grimby.

STUDIES IN CEREBRAL ŒDEMA AND CEREBRAL SWELLING

I. The Changes in Lead Encephalopathy in Children Compared With Those in Alkyl Tin Poisoning In Animals

BY

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(This investigation was assisted by Grant B.483, National Institutes of Health, Division of Neurological Diseases and Blindness)

This is the first of a series of papers in which we endeavour to state what is known about the morphological changes in a variety of conditions in which there is an increase in the volume or water content of the brain. The final paper will summarize and we hope justify the nomenclature used and the plea for treating the whole subject in as simple a way as possible as far as the morphological aspects are concerned without premature abstraction. We think the latter has confused issues in the past and is still doing so today. It will be necessary finally to consider the history of the concepts about this subject in detail. For the present, however, we merely state the basis of our nomenclature and proceed with our observations. The term *cerebral swelling* is used to indicate an increased volume of the brain without commitment as to its nature and the term *cerebral œdema* to indicate an increase in the intracerebral water content. In some instances the latter has been determined, e.g. by Stewart-Wallace (1939) in the œdema around tumours, and by Magee, Stoner and Barnes (1957) in the œdema of alkyl tin poisoning. In other examples the existence of such an increased water content is inferred from the histological appearance. It should be emphasized that within these definitions, cerebral swelling may be associated with cerebral œdema in some circumstances, e.g. the œdema around tumours or one may occur in the absence of the other. It is further proposed that the term *exudative œdema* be used to indicate the presence of a protein-containing fluid in the extracellular tissue and *transudative œdema* when no protein or other macro-

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molecular material is present. In the present paper we describe the changes in lead encephalopathy in children as an example of exudative œdema and cerebral swelling, and of those in alkyl tin poisoning in animals as an example of transudative œdema. If the latter is severe both cerebral and spinal swelling are present.

Lead Encephalopathy in Children

An excellent account of the changes in the brain in this condition is that of Blackman who in 1937 gave a detailed description of the microscopical changes in the brain as well as some account of naked-eye features, the clinical picture and the historical background. This was based upon an analysis of material from 22 cases. He emphasized the presence of a patchy extravascular exudate about vessels, sometimes extending into adjacent tissue, and of evidence of recent and more remote damage to vessel walls. These changes were found in the cerebrum and cerebellum, and alterations in nervous tissue were thought to be secondary to the exudates. Occasional severe changes in the folia of the cerebellar cortex were noted. Since that time little has been added to our knowledge of the morphological changes.

The present account is based upon 16 fatal cases of lead encephalopathy occurring in Cincinnati between 1948 and 1957. In 4 of these the brain was examined in the fresh state in the autopsy room by one of the authors and numerous histological preparations had been made in 8. In the remainder, the number of sections available was more limited but sufficient to confirm some of the characteristic features. For the sake of brevity only 6 individual case histories are given and this is followed by a general account of the pathology with particular reference to these 6 cases. In all instances the final illness was acute and of short duration; in some there were indications in the history of previous episodes of poisoning of lesser severity. The age of onset was between 1 and 4 years of age in all except Case 5 which was in a 7-year-old white boy. In this child, a definite history of the mode of poisoning was not obtained, in the others there was evidence of ingestion. In every case there was some confirmation of the diagnosis by laboratory or radiological investigations, or both, and by post-mortem tissue analysis. Many received treatment with BAL or chelating agents, yet the dominant clinical feature was usually increased intracranial pressure and acute cerebral swelling. In more recent years, the treatment of this by massive craniectomy with decompression has been carried out in Cincinnati. An account of this procedure, given by McLaurin and Nichols (1957) includes more extensive clinical details of 2 cases of the present series.

Case Reports

Case 1.—This was a 3½-year-old coloured boy who had ingested putty in previous months. The terminal episode lasted four days, right-sided convulsions occurring two

days after the onset of vomiting and abdominal pain. Semi-coma then developed with a rapid rise of intracranial pressure (from 140 to 600 mm.) as measured by lumbar puncture. A right-sided decompression produced some improvement, but deterioration and death followed eighteen hours later. Positive stigmata of lead poisoning were a Hb. of 6·5 grammes/100 ml., coproporphyrinuria, suggestive lead lines in the bones, and opaque material in the colon on radiological examination. The blood lead was 0·26 mg./100 ml.

Case 2.—This 23-month-old coloured boy had a history of pica including the eating of paint from window sills. The final illness lasted about three weeks. It was initiated by a convulsion, then a period of lethargy, fever and vomiting followed by twitchings of the face and left arm on the day of admission. Laboratory investigations revealed a Hb. of 12·5 grammes, coproporphyrinuria, stippled red cells, lead lines in the ends of long bones, and a blood lead of 0·22 mg./100 c.c. Following a lumbar puncture which yielded C.S.F. with a pressure of 530 mm. and a protein of 69 mg., right and left-sided craniectomies were done, but the bone flaps were left in place after removal of dura, polyethylene sheets being interposed between the brain surface and the bone. Convulsions persisted on the day after operation, but were controlled by barbiturates. On the third post-operative day the child's temperature rose to 107°; he remained in deep coma that day and died early in the morning of the fourth day following respiratory distress.

Case 3.—This coloured boy, 21 months old, with a history of pica was admitted to the hospital after a minor fall. Convulsions occurred in the admitting ward and continued, the C.S.F. pressure being 240 mm., and the protein 50 mg./100 c.c. The day after admission the following stigmata of lead poisoning were identified: lines in the X-rays of the long bones, a blood lead of 0·23 mg./100 ml., coproporphyrinuria, and basophilic stippling of erythrocytes. Although therapy with EDTA produced some improvement for twenty-four hours, convulsions then reappeared and the child was less responsive. A right-sided decompression was therefore done on the third day after admission, and a left-sided one on the fourth day. There was improvement in the cerebral state, but on the second post-operative day gastro-intestinal bleeding, which necessitated blood transfusion, occurred. On the sixth post-operative day, tarry stools were again noted and the boy died on the seventh day after vomiting a large amount of bright red blood.

Case 4.—This 2-year-old coloured girl had a previous history of eating dirt, but had otherwise been well until three weeks previous to admission when she became listless and irritable. Her appetite decreased and two days previous to admission she had vomiting episodes. On the morning of the day the child entered the hospital, she had convulsions, mainly on the right side. On examination in the receiving ward, the girl was comatose; the pupils dilated, equal and not reacting to light. Lumbar puncture yielded fluid with a pressure of 600 mm. and a protein of 83 mg. per cent. X-rays showed lead lines at the ends of the long bones. Treatment with intravenous versenate, hydrocortisone, and ACTH produced no improvement and the pulse slowed. A right parietal craniectomy was done that evening, and the brain was so swollen that it became lacerated as it herniated through the dural opening. During the operation the condition remained poor with the pulse-rate varying between 60 and 160. The child expired some hours later as preparations for the second craniectomy were under way.

Case 5.—The patient was a 7-year-old white boy. No history to suggest lead ingestion was obtained but few details were available. It was stated that he had been in good health until the day before admission when he complained of nausea and vomiting, and fell when he tried to walk. On the day of admission he began to have

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convulsions on the right side, and was comatose when seen at the hospital. Papill-œdema was present, abdominal reflexes absent, bilateral Babinski responses were elicited, and a suggestion of a right facial weakness. On lumbar puncture the pressure of the C.S.F. was 360 mm.; it contained 10 lymphocytes and 85 mg. per cent of protein. The Hb. was 8 grammes but other investigations for lead poisoning were not performed. The seizures were controlled with barbiturates. In the evening the pulse-rate fell to 40 and a ventriculogram was done to exclude a space-consuming lesion. Soon after this he stopped breathing and the ventricles were tapped with removal of a small amount of fluid but there was no response.

Case 6.—This 2½-year-old white boy had a history of eating dirt and putty. He started to vomit two and a half weeks before admission; this became severe and was associated with anorexia and lethargy in the three days before entry to the hospital. At that time he was obviously ill but without indication of cerebral disturbance except for the undue lethargy. Investigations showed a Hb. of 7·8 mg./100 ml., stippled red cells, 4 plus coproporphyrinuria and lead lines in the long bones. Despite treatment with intravenous fluids and calcium versenate he deteriorated and developed dilated pupils as well as becoming more lethargic. A craniectomy on the right side was done the day after admission and on the left two days later, the intervening period being marked by convulsions and shallow respirations. He died on the day after the second craniectomy; in the terminal hours his pulse was very rapid and weak.

PATHOLOGY

Histological observations were mainly on paraffin-embedded material but in a few instances large celloidin blocks of cerebrum were available and frozen sections of brain were prepared for Cajal's gold chloride method in several cases. Analysis of tissues for lead was undertaken to some extent in all instances and the figures are recorded in Table I. The

TABLE I

Case	1	2	3	4	5	6
Bone	18·0	10·7	7·6	8·5		
Brain	1·06	·10		·28	·35	·17
Kidney				2·0		·88
Liver	3·65	·92	1·35	4·3		1·20

Lead concentration in mg. per 100 gramme of fresh tissue.

levels in the brain varied considerably, those in Cases 1, 4 and 5 being well above the "normal" range of ·01–·09 found by Aring and Trufant (1953) in cases in whom there had been no exposure to lead; those in Cases 2 and 6 were only slightly above this range.

None of the children showed evidence of malnutrition or of coincident severe infection although a few had patchy terminal pneumonia. In Case 3 the cause of the fatal alimentary hæmorrhage was erosion of the wall of an artery in the base of a duodenal ulcer which extended to the pancreas, and in Case 6 there was an irregular perforation in the lower third of the œsophagus which was associated with some necrosis of the adjacent mediastinal tissue. Histological examination, however, showed rather scanty inflammation compared with the extent of the necrosis

both in the wall of the œsophagus and the adjacent tissue. It is probable, therefore, that this perforation only developed shortly before death.

Microscopical changes were found in the kidney and spleen in all 6 cases. In the kidney a varying degree of tubular degeneration and regeneration with desquamation of some cells into their lumina was found. Intranuclear eosinophilic inclusions were present in the tubular epithelium, mainly in the inner cortex, to some extent in all examples. They were scanty in Case 5 and numerous in Cases 4 and 6 in which two they were also found in the liver. The diagnostic value of these inclusions was first described by Blackman (1936). Wachstein (1949) demonstrated that they could be acid fast. In our material this reaction was not always obtained. A more useful and consistent staining property was the marked positive reaction of the inclusions with aldehyde fuchsin or Schiff's reagent after sulphuric acid permanganate oxidation (fig. 1, Plate LXIV) which has been described by Landing and Nakai (1959) and attributed by them to a content of cystine.

In the spleen a consistent finding in these 6 cases, and in all the others reviewed except one, was the presence of reaction centres in the malpighian bodies. They were also found in lymph glands of those cases in which this tissue had been examined. In such reaction centres the follicle contains numerous histiocytes with eosinophilic cytoplasm, few blast cells and usually no mitotic figures (fig. 2). They are thought to be the end stage of germ centres. Their significance is discussed later (p. 421).

The naked-eye changes were most impressive in the central nervous system. In all cases there was pronounced cerebral swelling indicated by flattening of convolutions, obliteration of sulci and compression of the ventricles (fig. 3) except in Case 6 where they were slightly dilated. Uncinate and tonsillar herniation of moderate degree was usually present and in Case 6 the crowding of the posterior fossa with compression of the outlets from the fourth ventricle was thought to be the explanation of the slight ventricular dilatation. When craniectomy had been performed before death herniation was present at the site of operation. The weight of the brain was above the normal for the age in all (Table II) except Case 3 in which the head was small. As all other features in this case

TABLE II

Case	1	2	3	4	5	6
Age in years ..	$3\frac{1}{2}$	2	$1\frac{3}{4}$	2	7	$2\frac{1}{2}$
Sex	M	M	M	F	M	M
Weight of brain ..	1,215	1,100	830	1,230	1,275	1,300
Water content ..	74·6 white 82·5 grey					80 white 84·1 grey

Weight of brain in grammes at post-mortem and percentage of water in white and grey matter in Cases 1 and 6. Case 3 probably had mild micrencephaly before the final illness.

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indicated cerebral swelling it was thought that a mild micrencephaly had been present before the final illness.

On sectioning the cerebrum the usual finding was a dry cut surface, a normal demarcation between grey and white matter and a normal tint of the latter. In a few cases there were patches of blotchy red discoloration and even minute hæmorrhages. Thus in Case 4 the herniated right cerebrum showed this appearance in the cortex, the thalamus was affected on both sides and the lower parts of both temporal lobes, more particularly the right. A few similar patches were present in the tegmentum of the pons and in the cerebellum. In Case 6 the cortex adjacent to the hernia grooves at the site of the right craniectomy showed similar blotchy congestion.

The only other naked-eye change of note was the presence of a few shrunken folia at the borders of the cerebellar hemispheres in Cases 4 and 5, the superior edge being affected in Case 4 and the inferior in Case 5.

A summary of the microscopical changes in the nervous system is in Table III. In the cerebrum they were most severe in Cases 4 and 6. In the former there was evidence of extensive early patchy necrosis in the cerebral cortex and thalamus; in the latter a few areas of cortex were

TABLE III

Case	*Cerebrum*		*Blood vessels*	*Cerebellum*	*Other parts*
	Grey matter	*White matter*			
1	Slight neurone injury P.V.E.	P.V.E.	Basophilic deposits in walls	Focal atrophy and gliosis	
2	Slight neurone injury P.V.E.	P.V.E. Astrocytic prolif.		Focal atrophy and gliosis	Astrocytic prolif. in optic chiasm
3	Focal neuronal necrosis, e.g. in Ammon's horn	Astrocytic prolif.		Degen. of granular layer	
4	Patchy necrosis P.V.E.++	P.V.E.++ Exudate apart from vessels		Severe patchy atrophy of cortex	P.V. hæmorrhages in thalamus
5	Slight neurone injury P.V.E.	P.V.E.	Basophilic deposits in walls	Severe patchy atrophy of cortex	
6	Patchy necrosis P.V.E.	P.V.E. Increase in oligo-dendroglia		Focal atrophy	

Summary of histological changes in brain in Cases 1–6.
P.V.E.=perivascular exudation.

similarly affected, the changes in both being in those areas showing the blotchy discoloration to the naked eye. In these the neurones were shrivelled and surrounded by "halos" (? perineuronal spaces) (fig. 4). In the remaining 4 cases patches of degenerate and necrotic neurones in the cerebrum were scanty, e.g. necrotic groups in the dentate fascia in Case 3. In the cerebellum changes were slight in Cases 3 and 6 but marked in the remainder. In the atrophied folia noted with the naked eye in Cases 4 and 5 there was destruction of Purkinje cells and of the granular layer (figs. 5 and 6) in the depths of a few sulci. Round cell infiltration was present in the overlying meninges. In Case 1 there were foci of atrophy of the molecular and granular layers as well as marked gliosis in the cores of a few folia, and in Case 2 a patchy loss of Purkinje cells, mild degeneration of the granular layer, marked capillary dilatation in the molecular layer and astrocytic proliferation in the white matter.

Perivascular exudative œdema was present to some extent in the cerebrum and hind-brain in all examples apart from Case 3 (in which there had been a sufficient interval between craniectomy and death for reabsorption to occur). Case 2 was typical in showing exudate staining like blood serum both within the reticulin framework of the vessel wall and in some places outside it (fig. 7). In Case 4 the exudate was more extensive and lay around larger vessels. The Periodic Acid Schiff stain was useful in demonstrating the exudate in neural tissue and in Case 4 it showed it clearly in the deeper cortex and white matter apart from vessels. In some cases dilated perivascular spaces did not contain stainable exudate, e.g. some parts of the cerebrum of Case 5 (fig. 8).

Focal basophilic deposits in vessel walls, attributed by Blackman to old inspissated exudate, were found in Cases 1 and 5. In the former they were especially prominent in cortex, in occasional meningeal arteries (fig. 9) and in small capillaries in the cerebellum. In a few instances the vessel wall was stippled and in some the appearances suggested that diverticula had formed. Small linear streaks and spheres of this material were thought to represent obliterated capillaries, some of these being in direct continuity with neurones. In both cases a positive reaction for iron was given by this material but in only one section was a reaction for calcium positive.

Limited investigations on the water content of the brain were carried out in Cases 1 and 6; they show some increase in both grey and white matter (Table II). In no case was there any suggestion of pallor of myelin staining in the white matter similar to that seen in the œdema around cerebral tumours or in alkyl tin poisoning in animals.

Astrocytic proliferation in the white matter was found in Cases 2 and 3 (fig. 10), those in which life continued after craniectomy for several days; in Case 2 it was also found in the optic chiasm. Many axis cylinders and myelin sheaths in the central white matter showed focal swelling.

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Changes in oligodendroglia were not conspicuous. In the necrotic areas there was acute swelling of several and in Case 6 an apparent increase in their number in the vicinity of vessels in the white matter.

Summary and Significance of Pathological Changes

From the observations detailed above and less extensive ones made on other cases it is evident that subclinical cerebral episodes can occur with severe focal damage to the cerebellar cortex, to the walls of medium-sized and small vessels but not necessarily with significant cerebral damage. In the final illness the main damage may be to walls of vessels in the brain and meninges with accumulation externally of a serum-like exudate and marked dilatation of the perivascular spaces. It is possible that many of the latter contain a non-protein exudate which leaves no trace in the prepared sections. However, in such cases the cut surface of the brain appears dry so that the extravascular fluid, whether protein-containing or not, is held in a solid phase. Slight focal cellular infiltration, chiefly lymphocytic, is sometimes present about vessels in the meninges and brain. In examples that survive such severe episodes for some days evidence of damage to neural tissue is shown by the mild astrocytic reaction. Although focal swelling of axis cylinders and myelin sheaths is common, there is no pallor of myelin staining or separation of the sheaths such as occurs in the œdema around tumours and in that of alkyl tin poisoning. In occasional cases the picture is complicated by severe early patchy necrosis of the cortex and even of the deeper structures (e.g. Case 4). It is possible that this is brought about by pressure upon already damaged arteries and arterioles by the swollen brain producing a vicious circle. Lindenburg (1955) has illustrated such a mechanism in certain traumatic cases. When, however, necrosis of groups of nerve cells is very focal, e.g. Ammon's horn in Case 3, the convulsions may well play an ætiological role. Those examples in which the necrosis is considerable may be the ones in which handling produces disintegration of the cerebrum in the operating or the autopsy room and in which, in description, the brain has been compared to toothpaste. The cut surface may then be "wet" but we have not handled such a specimen in the fresh state.

Alkyl Tin Poisoning in Animals

Accounts of the toxicity of these compounds for various animals are in the papers of Caujolle, Lesbre and Meynier (1954) and Stoner, Barnes and Duff (1955). A detailed account of the histological and chemical changes produced in the central nervous system of the rat by feeding tri-ethyl tin compounds has been given by Magee, Stoner and Barnes (1957). A striking interstitial œdema of the white matter of the brain and spinal cord without apparent neuronal damage was produced after feeding 20 parts per million of the compound in an ordinary rat diet, the early stages

being manifest after six days, and the fully developed lesions after fourteen days at which time a paraplegia became evident. This was followed by quadriplegia and death if the diet was maintained, but if the amount fed was reduced to 10 parts per million clinical recovery occurred although the anatomical changes progressed. If the toxic substance was removed from the diet some weeks before killing the animals, however, the anatomical changes regressed.

We repeated these feeding experiments in rats using a higher dosage of tri-ethyl tin hydroxide (40 parts per million in some animals, 80 parts per million in others) and were able to confirm the occurrence of a striking interstitial œdema (figs. 11 and 12) after ten to fourteen days, at which time paraplegia followed by quadriplegia and death was observed in a number of the animals; clinical and anatomical recovery followed in those from whom the poison was then removed. In those dying or killed with the fully developed lesions the volume of the spinal cord appeared to be increased; this was not conspicuous in the brain. Our feeding experiments in dogs were for various reasons not successful, but by repeated intravenous injections over a period of four to five weeks in two animals similar but not such marked lesions were produced in the white matter. In the first of these approximately 1 mg./kg. of tri-ethyl tin acetate was injected every few days for thirty days; in all 10 injections were given and the dog was killed on the thirty-fourth day. A short period of apnœa sometimes followed the injection and stupor or loss of consciousness persisted for as long as half to one hour. During this period electroencephalograms were sometimes taken but they showed no significant change. After the first few days the dog became irritable and somewhat listless; at the end of two weeks the gluteal muscles were wasted and activity was slight, the animal spending most of the time lying in his cage although he could be stimulated to walk. This state persisted until the day of killing, the wasting of the gluteal muscles becoming more marked. In the second dog the dosage was similar, 2 injections, approximately 1 mg./kg. being given over a period of twenty-five days and the animal killed on the twenty-ninth day. He became very agitated and ataxic for a short time after each injection but was not unconscious. On a few occasions a subsequent injection of nembutal was given in order to obtain an electroencephalogram; again these showed no significant abnormality.

At necropsy changes were confined to the central nervous system and here there was no marked swelling of the brain and cord. On section of the brain after fixation the white matter was prominent but the ventricles were not obviously compressed, nor the sulci narrowed. On microscopic examination the myelin sheaths were separated by spaces (figs. 13 and 14) throughout the white matter of the cerebrum, hind-brain and cord. It is presumed that these corresponded to fluid-containing

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areas before processing of the tissues and that, as no macromolecular material was demonstrable in the spaces the fluid was mainly water. In one of the dogs and several of the rats injection of trypan blue into the vascular system shortly before death failed to demonstrate any break in the blood-brain barrier. This point was investigated in more detail by Magee, Stoner and Barnes (1957) in their rat experiments, using the distribution of sulphanilamide between central nervous tissue and plasma, and the distribution of ^{32}P as well as dye methods. They concluded that tri-alkyl tin compounds did not greatly alter the permeability of the barrier. Their chemical analyses indicated that the affected tissue contained increased water and sodium but a normal amount of potassium.

Summary of Changes

By feeding in rats and repeated intravenous injection in dogs of tri-ethyl tin compounds a striking interstitial œdema of the white matter is produced. From the absence of macromolecular substances in this œdema it is considered to be a transudate rather than an exudate. There is no evidence that it is associated with damage to the blood-brain barrier. In the rats the œdema was sufficiently severe to produce increase in volume of the spinal cord (? spinal swelling). Magee, Stoner and Barnes (1957) claimed a detectable increase in the volume of the brain in rats; to us this was not obvious, nor could we detect it in the dogs. It is probable that the readily apparent spinal swelling is a reflection of the greater volume of white matter in the rat spinal cord compared to the rat brain. If our lesions in the dog had been of comparable severity to those in the rats an increase in the cerebral volume would have been expected.

Discussion

We have endeavoured to give enough detail in description to justify the use of the term exudative œdema and cerebral swelling in the consideration of lead encephalopathy and transudative œdema in tri-ethyl tin poisoning. In the case of lead further complicating lesions such as cerebellar atrophy and focal cerebral necrosis may occur, which are not seen in the tin experiments. It is worth while to sum up what is known and unknown about the pathogenesis of these contrasting lesions.

While the cerebral swelling is the dominant feature to clinician and pathologist in the fulminant stage of lead encephalopathy the anatomical changes indicate both a widespread disease and often older damage to the nervous system. As regards the former we would only mention that the intranuclear inclusions in kidney and liver probably reflect a significant deviation of metabolism on a nuclear level and that this may be more widespread than the detectable distribution of such inclusions indicates. Whether the degenerative lesions of renal tubular epithelium found in

lead poisoning are related to the aminoaciduria which is a feature of the disease is unknown at present.

The principal site of central nervous system lesions antedating the final episode is the cerebellum. The most striking lesion here is the atrophy of folia and its focal distribution suggests a vascular determination of the localization. The basophilic material in the walls of medium-sized and small arteries and even capillaries indicates that severe vascular damage can occur in earlier stages of the disease. It would therefore appear that damage to the blood-brain barrier can occur both before and during the final episode. The serous exudation which is characteristic of the latter may be the cause of the cerebral swelling but it is not always so extensive in microscopic preparations as to convince one that it is the only factor. This applies both to those examples without cerebral necrosis and to those in which the latter has occurred either as a result of vascular damage by lead or from the superadded vascular compression promoted by the initial swelling. It is therefore possible that the lead acts on some other component of the nervous system, e.g. myelin, to produce increase in volume in some unknown way. At present, however, there is no evidence to support this speculation.

Whether a condition comparable to lead encephalopathy in children has been produced in animals is not entirely clear. The earlier experiments of Ferraro and Hernandez (1932) were performed by feeding and intravenous injections in cats and monkeys of inorganic lead compounds. They produced changes in nerve cells and astrocytes but not apparently a state similar to that occurring in these children. Pentschew (1957) has produced violent cerebral symptoms in rabbits by injecting repeated sublethal doses of lead acetate into the cisterna magna.

He suggests that sensitization of the brain against lead may be the explanation of these symptoms and refers to the observations of Baader (1954) in human subjects in support of this hypothesis. The latter author attempted to cure cases of chronic lead poisoning with small doses of lead and found that exacerbations were produced with extremely small doses.

The observations recorded here suggest that an immunization hypothesis deserves further consideration. In support of this we may cite the evidence of earlier damage to the brain in several cases and the fact that in some ways the final episode of encephalopathy has the character of a severe local anaphylactic reaction dominated by exudative œdema. Furthermore, the lesions in the malpighian bodies of the spleen which we call reaction centres are probably a manifestation of antigenic stimulation. In some ways they resemble the lesions described by Germuth (1953) in rabbits injected with a single dose of crystallized bovine albumin. We hope to investigate the effects of lead salts combined with erythrocyte

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stroma and adjuvants to see if further evidence in support of the immunization hypothesis can be obtained.

The cause of death in many examples of lead encephalopathy is not clear. We have assumed the duodenal ulceration which led directly to death in Case 3, and the œsophageal perforation which was perhaps merely a part of the terminal stage in Case 6 to be due to autonomic dysfunction. This, of course, was the explanation given by Cushing (1932) many years ago for similar alimentary changes associated with intracranial lesions. However, such dramatic lesions were not found in the other cases; nor was there convincing clinical evidence in these of any constant autonomic dysrhythmia in circulation or respiration. Although mild tonsillar and hippocampal herniation was observed in several instances, the former did not appear to be severe enough to have caused medullary compression and the latter was not associated with brain-stem hæmorrhage or necrosis.

The interstitial œdema produced by tri-ethyl tin by contrast appears to be unassociated with evidence either of anatomical damage to the walls of cerebral vessels or of any alteration of the blood brain barrier that can be revealed by studies with dyes and ^{32}P. The mechanism by which the excess of water and sodium is retained in the tissues is completely unknown at present. Also unknown are the reasons why in rats the first gross neurological deficit appears in the hind-limbs—a failure of conduction first becoming manifest in the longer fibres is a possibility—and why the excess water is limited in its distribution to the white matter of the central nervous system. We do not propose to speculate further about the physiological disturbance except to comment that our lesions in dogs were not so severe as those in the rats. We cannot therefore assume that paraplegia and quadriplegia could not be produced in dogs with this toxin. The occurrence of gross defect appears to depend to some extent on the rate at which the œdema is established as in some animals no deficit occurs despite anatomical changes and in others recovery occurs on reduction of the dose of tin although anatomical changes persist. Magee, Stoner and Barnes (1957) suggest that adaptation occurs to the fluid bathing the fibres.

The limitation of the fluid to the white matter of the central nervous system suggests that the mechanism does not involve myelin which is also present in peripheral nerves, or glia cells which are also found in grey matter. The histological appearances suggest that there are potential interstitial spaces in the white matter, in which excessive fluid has accumulated. The degree to which the "normal" appearances return in the animal which has developed paraplegia, and has then been taken off the diet with clinical recovery, gives strength to the idea that some such system of spaces containing a minimal amount of fluid exists in the untreated rat and probably in the dog. How the fluid is limited to the white matter is again an unknown fascinating problem.

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Hess (1953) has produced evidence from histochemical investigations for a "ground substance" in the grey matter but not the white matter. The work of Wyckoff and Young (1956) with the electron microscope does not support this concept. If there is no anatomical structure limiting the spread of water it would be necessary to search for evidence of electrical fields limiting the hydration or some other unknown mechanism. The tri-ethyl tin compounds may be of great use in further neurophysiological investigation. They have certainly been of value in giving us a morphological picture of cerebral transudative œdema with which to compare the changes in such human diseases as lead encephalopathy, and to give point to the variety of mechanisms which may operate in cerebral swelling.

Summary

In an initial paper dealing with the morphological changes in cerebral œdema and cerebral swelling the changes in lead encephalopathy in children and in alkyl tin poisoning in animals are compared.

In the former the brain shows some evidence of vascular damage with patchy exudative œdema. This is probably the main factor in producing cerebral swelling but may not be the only factor. In severe cases patchy cerebral necrosis may be due to pressure upon arteries by the swollen brain. Small foci of older damage, particularly in the cerebellum, are often present without clinical manifestations.

In contrast, alkyl tin compounds in rats and dogs produce a striking interstitial œdema confined to the white matter of the central nervous system but there is no evidence of vascular damage.

The pathogenesis of these two conditions is briefly discussed.

ADDENDUM

Since this paper was written Torack, R. M., Terry, R. D., and Zimmerman, H. M. have published an account of the swelling produced by tri-ethyl tin in the mouse (*Am. J. Path.*, 1960, **36,** 273) in which they claim on the basis of electron microscopic observations that the œdema fluid is present in glia cells. This is regarded as supporting evidence for the view of Lumsden, C. L. (Proceedings, Second International Conference on Neuropathology, London. Excerpta Medica Foundation, Amsterdam, 1955, 373), that fluid transport in the brain is an intracellular function and that the astrocyte was the cell involved. Many physiologists and biochemists, however, still find the concept of an extracellular space desirable to explain fluid transport in the brain.

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LEGENDS FOR PLATES

PLATE LXIV

FIG. 1 (*Case* 4)—Intranuclear inclusions in kidney. Sulphuric acid permanganate followed by aldehyde fuchsin. × 650.

FIG. 2 (*Case* 4).—Reaction centre in malpighian body of spleen. H. and E. × 160.

FIG. 3 (*Case* 2).—Flattened convolutions, narrow sulci and compressed ventricles.

PLATE LXV

FIG. 4 (*Case* 4).—Necrosis of cortical neurones. H. and E. × 160.

FIG. 5 (*Case* 4).—Destruction of Purkinje cells and granular layer in cerebellar cortex. H. and E. × 50.

FIG. 6 (*Case* 5).—Destruction of Purkinje cells and granular layer in cerebellar cortex. Round-cell infiltration in meninges. H. and E. × 650.

FIG. 7 (*Case* 2).—Exudate staining like serum in perivascular space of white matter. PAS × 160.

FIG. 8 (*Case* 5).—Dilatation of perivascular spaces in white matter. H. and E. × 90.

FIG. 9 (*Case* 1).—Basophilic deposit in meningeal artery. Small flecks in cortex. H. and E. × 160.

PLATE XLVI

FIG. 10 (*Case* 2).—Astrocytic proliferation in subcortical white matter. Death three weeks after onset. Cajal's gold chloride sublimate. × 160.

FIG. 11.—Interstitial œdema in white matter of spinal cord of rat ten days after feeding with tri-ethyl tin hydroxide. The nerve roots are not affected. Kluver's stain. × 30.

FIG. 12.—Cerebellum of similar rat to that in fig. 11. Marked œdema of white matter but no involvement of granular or molecular layer. Kluver's stain. × 90.

FIG. 13.—Interstitial œdema in cerebral white matter of dog given tri-ethyl tin acetate intravenously for thirty days. H. and E. × 650.

FIG. 14.—Interstitial œdema in white matter of spinal cord of dog given tri-ethyl tin acetate intravenously for thirty days. Posterior columns above central canal. Kluver's stain. × 100.

FIG. 15.—Normal dog spinal cord—control for fig. 14. Kluver's stain. × 100.

PLATE LXIV

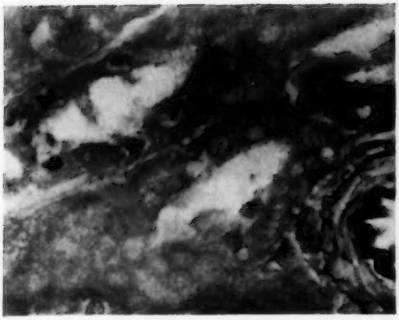

FIG. 1.

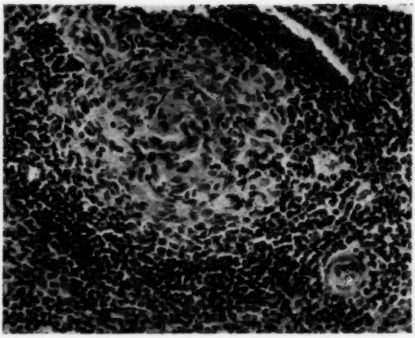

FIG. 2.

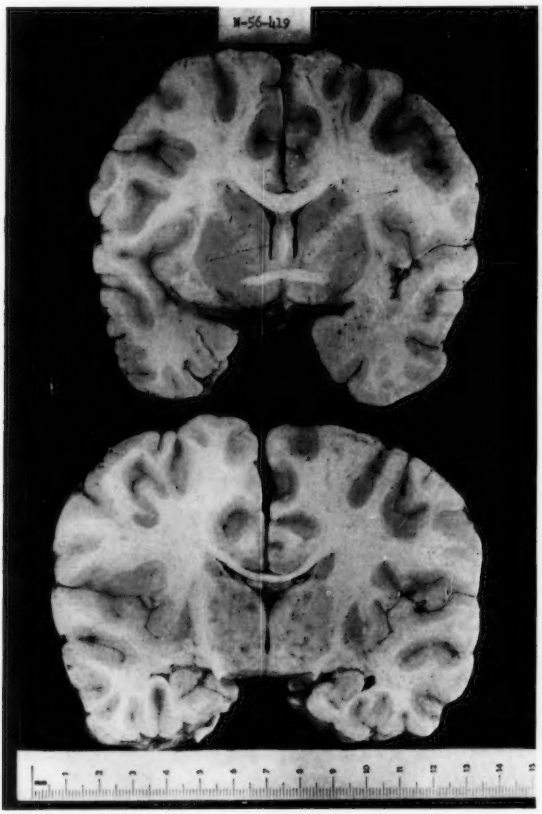

FIG. 3.

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PLATE LXV

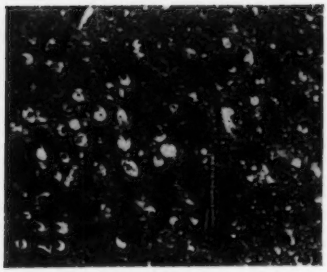


FIG. 4.

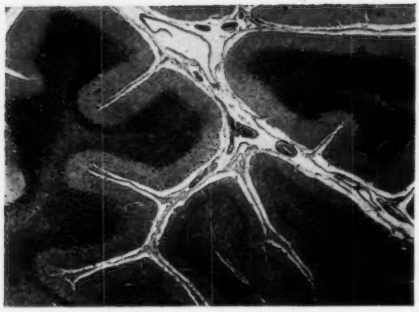


FIG. 5.

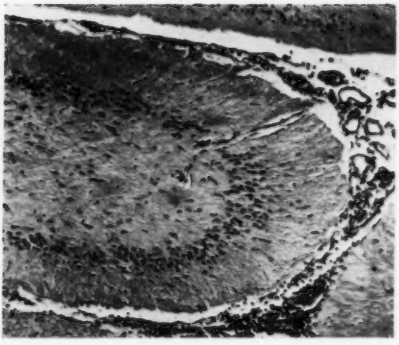
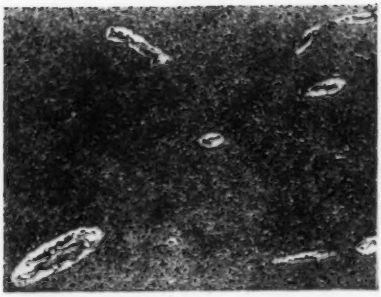


FIG. 6.

FIG. 7.



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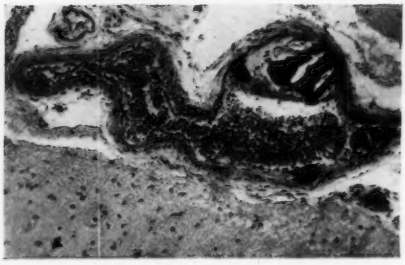

FIG. 9.

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FIG. 10.

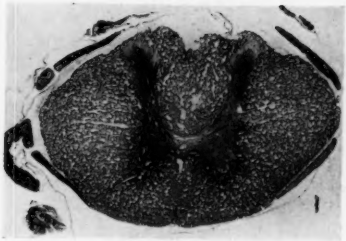

FIG. 11.

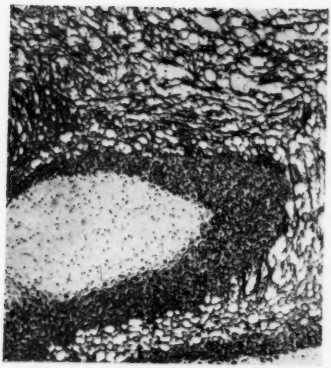

FIG. 12.

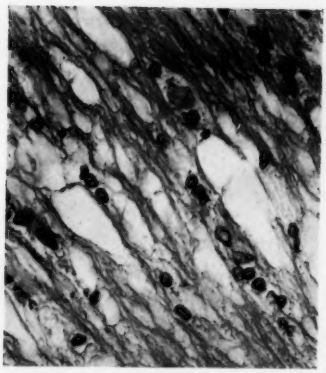

FIG. 13.

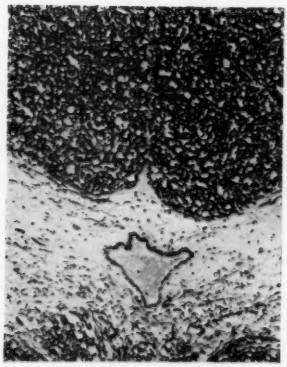

FIG. 14.

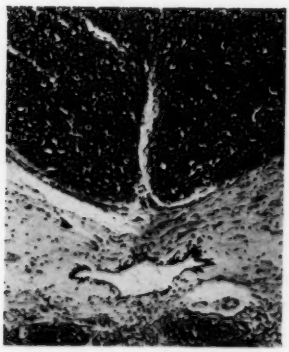

FIG. 15.

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VENOUS SIGN IN CEREBRAL ANGIOMA

BY

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PRE-ANGIOGRAPHIC diagnosis of an angioma is not always made and the condition may not be suspected for several years after the onset of fits or of headaches. In this paper a hitherto unrecorded physical sign is described and discussed. This sign when present makes clinical diagnosis more certain but like any other physical sign its significance is more valuable when accompanying other manifestations of the disease.

The elicitation of the sign is based on the fact that an angioma is an arteriovenous malformation. Under such conditions the arterial blood is driven at great pressure directly into veins, which unused to the high pressure dilate since there is no interposition of a capillary bed to break down the pressure of the arterial blood before it reaches them. If the draining vein is obstructed manually, the part between the shunt and the obstructing finger dilates considerably and visibly—the filling being very rapid and much faster than in an ordinary vein which has been manually obstructed. It was thought that the same would apply in the case of a cerebral angioma but with certain differences which were due to the special character of the shunt, the complexity of the cerebral circulation, and the impracticability of compressing the immediate draining veins from the angioma. However as most of the venous blood from the brain is carried through the internal or external jugular veins (Shenkin, Harmel and Kety, 1948), it was believed that manual obstruction of these would cause excessive and rapid filling of these veins which would be easily visible in the presence of an angioma, but not in normal individuals. Accordingly the following test was devised.

The patient is sitting upright or better still propped up at an angle of approximately 45 degrees with the bed, looking straight ahead, the neck is completely bared, and it is ascertained that the light is equally distributed over the neck. Then pressure is exerted with either the finger tips or the radial border of the index finger on either side separately and then both sides simultaneously (Plates LXVII, LXVIII, figs. 1–3). Low down in the

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neck just above the clavicles the external jugular vein is fairly superficial and can be easily obstructed. As the internal jugular vein is deeper, greater pressure is required and this is best done at the medial border of the sternomastoid or between its two clavicular heads (fig. 2). The obstruction being applied, one watches the venous filling cephalic to the pressure. As the external jugular is superficial the filling is easy to see (fig. 1). In the case of the internal jugular the venous engorgement is best seen by a considerable and rapid fullness appearing below and behind the angle of the jaw, where the vein is relatively uncovered by the sternomastoid. It can also be seen lower down in the neck as a large bulge pushing the sternomastoid forward (figs. 2 and 3).

Normal Response

In order to ascertain what was the normal response to this test a hundred normal individuals were selected from all age groups. Some were medical students; the rest were patients with minor and insignificant complaints. No patient with cerebral, cardiac or respiratory disease was selected, nor any with clinically raised jugular venous pressure.

It was found that in such a group, the internal jugular became visibly full in only 3 out of 100, the filling being slow in every case. The external and anterior jugulars became visibly prominent in 7 individuals, but again the filling was never rapid and the veins never became turgid as in the presence of arteriovenous malformations. The filling was only moderate in 3 and slight in 4. In the rest of the individuals pressure of the veins at the root of the neck produced only slow and slight filling. Hence in otherwise normal individuals the chances of a false positive test are very low.

Venous sign in cerebral angioma.—17 patients with proven cerebral arteriovenous malformations (angioma) attending the Neurological Department of The London Hospital were examined. Most angiomas were of fair size; the knot of tangled vessels measured on an average 4·7 cm. in its longest diameter on the lateral angiogram, the largest being 8 cm. long, and the smallest 1 cm. Patients with angiomas smaller than that were not available for study. Hence patients in this group had fairly large shunts and big draining veins as seen on angiography.

It was found that 6 of the 17 showed a strongly positive test. In 5 of these the venous engorgement was characterized by rapid filling of the neck veins on the ipsilateral side; in 1 it was more marked on the contralateral side; in those in whom it was bilateral the side where it was fuller and more rapid was considered positive. In 9 patients the venous filling was moderate, that is not as marked as in the first group, but still rapid and full enough to be called abnormal. It was on the same side in 6 patients, on the opposite side in 2 and equal on the two sides in 1 patient. In 1 central (thalamic) angioma the filling was on both sides, but more on

the right than on the left. This was a "moderate" positive response. Only in 1 patient was the sign completely negative.

3 illustrative cases are selected and although it is difficult to show the sign on photographs as it is the movement of the filling vein which has to be appreciated, an attempt has been made to do so.

M. A. (L.H. 42419/52). This patient had a large right parietal angioma. The venous sign was present on the ipsilateral side only. Both the right internal and external jugular veins filled much more rapidly than the left, the right external jugular becoming quite turgid as shown in fig. 1, where the contrast with the left external jugular is clearly seen. The right anterior jugular was also abnormally engorged (the anterior jugular is a part of the external jugular system). The abnormal external jugular filling is more impressive in this case than the internal jugular filling. The sign was considered strongly positive.

R. E. (L.H. 7815/55). The patient had a large parietal angioma on the left side but fed by the anterior cerebral arteries of both sides. On eliciting the venous sign, a large superficial vein, probably the left anterior jugular became prominent to the left of the mid-line. The internal jugulars became prominent on both sides but the left was more so than the right. The sign was considered as moderately positive fig. 2).

H. H. (L.H. 10553/56). A patient with a left parietal angioma. In this patient the external jugulars became prominent on both sides equally. The filling was rapid and excessive but the veins did not become as turgid as in Case 1. Fullness of the internal jugular vein was seen on both sides practically equally or perhaps a little more prominent on the sides ipsilateral to the angioma. The sign was considered moderately positive (fig. 3).

Discussion

This is not an infallible sign to be found in every case of cerebral angioma. It is found only in the presence of angiomas with well-marked shunts. No statistical conclusions can be drawn from a small selected group, such as this. However, all but one showed an abnormal response. It may be difficult in the beginning to appreciate the "moderate" filling and to differentiate it from normal filling of the veins, but there should be no difficulty at all in recording the strongly positive test which in this small series was present in over a third of the cases. This physical sign then becomes as diagnostic of a cerebral angioma (or much more so if the moderate positives are also taken into account) as a cephalic bruit, the presence of which is reported to vary from 18 per cent to 80 per cent in various reported series (Wadia and Monckton, 1957).

Much work has been done on the cerebral circulation in the past decade. Shenkin, Harmel and Kety (1948) made some revealing observations with the use of dye injection technique on the venous side of the circulation. Conducting studies on normal human subjects they came to the following interesting conclusions:

(1) On the average, in the series of 5 cases, 66 per cent of the blood from a single carotid artery drained by the internal jugular veins appeared

in the ipsilateral internal jugular bulb, and 34 per cent appeared contralaterally.

(2) An average of approximately 22 per cent of the blood flowing in an external jugular vein is derived from ipsilateral internal carotid artery, and therefore, presumably a significant fraction of the contents of the external jugular vein is cerebral venous blood.

(3) Only 2·7 per cent of the blood in the internal jugular vein was derived from extracerebral sources.

(4) The great discrepancy between the figs. 2 and 3 indicates that the flow of blood in the cerebral–extracerebral pathways is predominantly away from the brain. In order that blood may pass from the facial circulation to the intracranial veins by way of emissary veins, it would have to travel against a large pressure gradient.

Nylin (1958) using entirely different methods of studying the cerebral blood flow by aid of labelled erythrocytes with thorium–B, came to the similar conclusions, that there is a certain amount of admixture of blood on the venous side of the cerebral circulation, and that the drainage from one side of the brain, whilst mainly ipsilateral is also contralateral to a smaller extent, and the mixing of blood is most probably in the sagittal sinus and transverse sinus.

Unfortunately, detailed studies, similar to those above have not been carried out on the cerebral venous return in cases of cerebral angioma. Whether it would be correct to assume that the presence of an angioma does not disturb the cerebral venous drainage is a matter for conjecture.

Whilst no observations have been carried out on the venous drainage, several interesting but small studies have been made on the cerebral blood flow in patients with cerebral angiomas. Shenkin, Spitz, Grant and Kety (1948) studied by the nitrous oxide method 2 cases of cerebral angioma and found that the cerebral blood flow was considerably increased to approximately three times the normal rate in the presence of an angioma. In either case the cerebral blood flow was increased on both sides of the brain, but in one it was more ipsilateral and in the other it was more contralateral to the angioma. Bessman *et al.* (1952) reported on 2 patients, in whom they studied the cerebral blood flow by a modified nitrous oxide technique. In both patients the rate of cerebral blood flow was markedly increased on the side of the angioma. In their first patient, it was also increased considerably on the contralateral side but not so much as on the side of the angioma. In the second patient, there was no contralateral increase at all. Bernsmeier and Siemons (1953), using the original Kety and Schmidt method studied 6 patients, but have unfortunately made no mention of the circulation of the contralateral side. In all their 6 cases the cerebral blood flow was increased ipsilaterally from one and half to nearly four times the normal. Lassen and Munck (1956) also studied 2 patients using radioactive Krypton 85. In 1 patient the cerebral blood

flow was increased strictly ipsilaterally, suggesting that the venous drainage was entirely unilateral and there was no admixture of blood at the confluence of sinuses (torcula Herophili). In the other patient the blood flow was bilaterally increased, but more on the side of the angioma. Thus it can be seen that in the 6 cases, collected from the literature where bilateral cerebral blood flow studies were done, the flow was increased more ipsilaterally in 5 cases, and contralaterally in 1, and also that it was bilateral in 4 out of the 6 cases although one side was more than the other.

Our own and others' experience from cerebral angiography in angiomas shows that (1) the cerebral blood flow is certainly faster than in normals, (2) there is considerable dilatation and engorgement of the cortical and deep cerebral veins. The great vein of Galen is often three times the normal size (fig. 4). The great vein of Galen drains into the straight sinus which opens into the torcula Herophili and then mostly into the left transverse sinus and into the left internal jugular vein. The cortical veins drain either via (1) the superior anastomotic vein into the sagittal sinus, (2) the inferior anastomotic vein into the transverse sinus, or (3) the superficial middle cerebral vein into the cavernous sinus, and from there into the transverse sinus or into the external jugular circulation via the pterygoid plexus and ophthalmic veins. The superior sagittal sinus opens mostly into the right transverse sinus, which then drains into the right internal jugular vein.

Bernsmeier and Siemons (1953) also studied the venous pressure in the superior jugular bulb, on the same side as the angioma and found it to be increased two to three times the normal. No study was carried out on the opposite side or in the external jugular system. A complete study of the venous pressures in both the internal and external jugular systems would also considerably help in explaining the sign.

It can thus be seen from the anatomical and physiological facts of cerebral venous circulation in normals and in patients with angioma that the sign must depend on (1) the ultimate venous drainage of the angioma, (2) the rate of cerebral blood flow.

If the veins drain into both the external jugular and internal jugular circulations, then both these veins will show a positive sign. If the drainage from the angioma is bilateral and the cerebral blood flow bilaterally increased then the venous engorgement will be on both sides. And again it may be more ipsilateral or contralateral, depending on which side the cerebral blood drains more and on which there is greater cerebral blood flow. The sign is usually ipsilateral.

Finally, it is not difficult to understand why the sign may be negative or weakly positive in some cases. If the shunt is not large, or if the arterial pressure built up at the shunt is wasted on a long and devious drainage through many cerebral veins to the internal and external jugular veins then the sign will be negative. Again unlike arteriovenous shunts of the limbs, it is impossible to obstruct and observe the filling of veins directly

XUM

draining the cerebral malformation. As the obstruction is applied at a vein at some distance from the shunt, in the neck, the sign may be negative at times.

An attempt was made to correlate the size of the angioma as measured on the lateral angiogram with the positivity of the sign. It was found that there was no direct association between the two. It appears that it is not the size of the angioma that matters. If the size of the shunt is big, the number of veins draining the angioma few, the blood flow fast, and most of the blood draining into one internal or external jugular system, then the sign will be strongly positive.

Summary

(1) A hitherto unrecorded sign of cerebral angioma has been described.

(2) It was shown that manual obstruction of the internal or external jugular vein in the presence of an angioma caused a rapid and considerable filling of these veins. The test was strongly positive in 6 out of 17 patients, being ipsilateral in 5. It was negative in 1 and moderately positive in the rest.

(3) 100 individuals were also subjected to the same test and it was found that the venous filling in the neck was seen in only a few individuals and that it was never rapid as in the presence of an angioma.

(4) The likely mechanisms operating to produce the sign are discussed.

Acknowledgment

My thanks are due to Sir W. Russell Brain, Mr. D. W. C. Northfield and Dr. R. A. Henson for allowing me to examine their patients and for their constant encouragement in the preparation of this paper.

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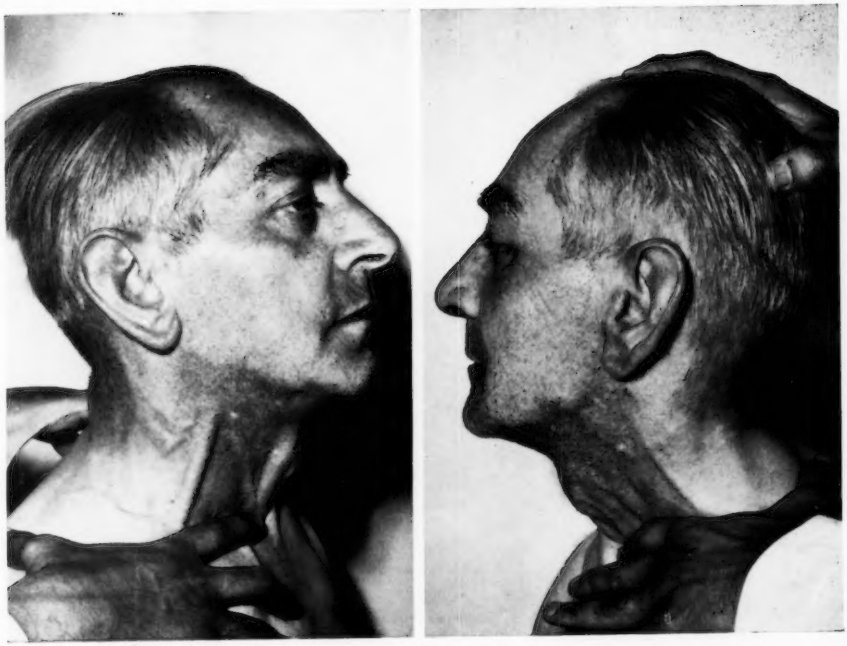

FIG. 1.

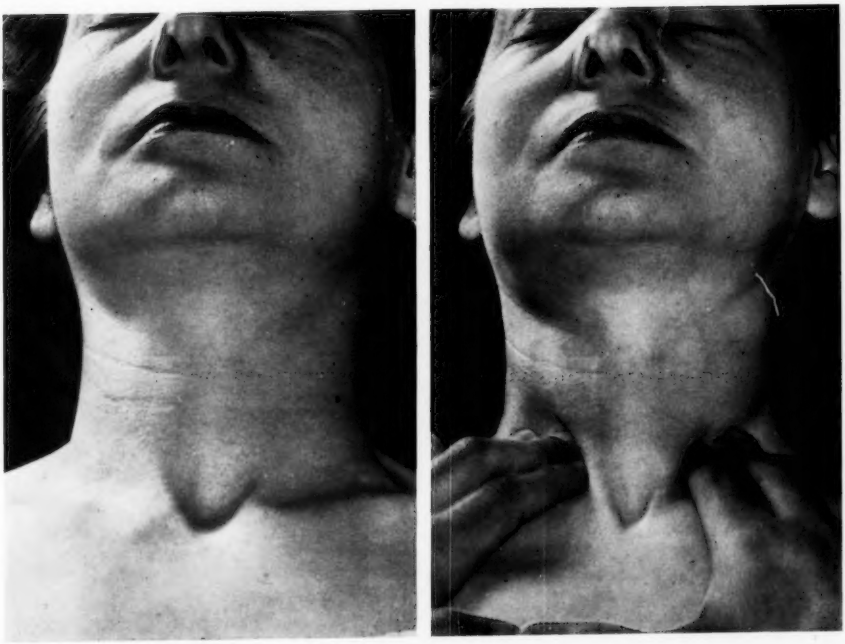

FIG. 2.

To illustrate article by N. H. Wadia.

PLATE LXVIII

FIG. 3.

FIG. 4.

To illustrate article by N. H. Wadia.

LEGENDS FOR PLATES

PLATE LXVII

FIG. 1.—Manual obstruction to the superficial jugular veins on the two sides produces a marked venous engorgement on the right side (external and anterior jugular veins) but not on the left. The sign is strongly positive.

FIG. 2.—Shows technique of compression of the internal jugulars between the two heads of the sternomastoids. Note the bulge which appears above the compressing fingers. It is more on the left. The angioma was on the left side. Of course, the rapidity of filling cannot be shown in a still photograph.

PLATE LXVIII

FIG. 3.—Another method of eliciting the sign. Notice the bilateral engorgement, perhaps a little more on the left than the right. The angioma was on the left side.

FIG. 4.—The large draining cortical vein and the vein of Galen are both at least three times the normal size in this angiogram of an angioma.

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PROGRESSIVE MUSCULAR DYSTROPHY OF THE DUCHENNE TYPE IN FEMALES AND ITS MODE OF INHERITANCE

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INTRODUCTION

MOST recent authors maintain that progressive muscular dystrophy in childhood of the classical Duchenne type is inherited as a sex-linked recessive character with a high mutation rate (Stephens and Tyler, 1951; Stevenson, 1953; Walton and Nattrass, 1954). This mode of inheritance would not explain the many female cases reported in the literature.

The main difficulty appears to be the difference of opinion on what constitutes muscular dystrophy of the Duchenne type. Stevenson (1953) lays down fairly rigid criteria for his "Duchenne-type rapidly progressive muscular dystrophy of young boys." He defines it as a disease with "(*a*) expression solely in the male, (*b*) onset mainly in the first two years of life, (*c*) high frequency of pseudohypertrophy of the calves, (*d*) universal affection of the gluteal, thigh adductors, and later scapulohumeral muscles, with (*e*) rapid progression to inability to walk usually before the age of 12, and death in the teens, the subjects seldom surviving to the age of 20." Walton and Nattrass (1954), while accepting the sex-linked recessive mode of inheritance, give the disease a wider latitude. They maintain that it may sometimes affect females and describe 3 such cases with typical pattern apart from a somewhat slower progression. They also include in the group cases of males with onset in the second or even third decade and a slower rate of progression.

If Duchenne-type muscular dystrophy were inherited only as a sex-linked recessive trait one would expect to find female cases only under the following circumstances:

(*a*) The mating of the carrier female with an affected male. There is no report of such a case in the literature. It is most unlikely that affected males will reproduce, although this may be possible in the milder form of the disease, and Walton (1955) records such a case, with typical distri-

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bution of muscular involvement but a slower progression, who had 4 normal children.

(*b*) The mating of a carrier female with a normal male who has undergone a mutation on the X-chromosome. This would produce a female who is homozygous for the mutant gene. On the assumption that the incidence of carrier females is the same as that of affected males (approximately 50 per million) and the estimated mutation rate for this disease in males (using Haldane's formula) is 43 per million, Walton (1956) estimated the incidence of affected females resulting from carrier mothers and mutant-containing fathers to be $50 \times 43 \times \frac{1}{2} \times 10^{-12}$—approximately one case per 1,000 million population or one case per 50,000 affected males. This is considerably less than the actual incidence of affected females.

(*c*) The mating of a carrier female with a normal male resulting in a female with Turner's syndrome and an XO sex-chromosome pattern, with the gene for muscular dystrophy on the X-chromosome. This seems to be the explanation in the unique case described by Walton (1956).

Becker (1953) suggested that the pelvic girdle or "ascending" form of muscular dystrophy could be inherited through a sex-linked recessive or an autosomal recessive trait, the latter tending to be more benign. More recently (Becker, 1957) he has subdivided the sex-linked recessive form into two distinct entities, which he believes are due to different genes. He thus defines three categories of muscular dystrophy with onset in the lower limbs:

(1) Malignant X-chromosomal type.
(2) Benign X-chromosomal type.
(3) Autosomal recessive type.

The malignant X-chromosomal type is equivalent to the classical Duchenne rapidly progressive type of childhood. The benign X-chromosomal type is similar in clinical pattern but has a slower progression and usually a later onset. The autosomal recessive type includes the limb-girdle type (starting in the pelvic girdle) of other authors (Stevenson, 1953; Walton and Nattrass, 1954) and also overlaps the benign X-chromosomal type in clinical picture.

The views of Blyth and Pugh (1959) closely parallel those of Becker. They divide childhood muscular dystrophy (cases manifesting before the age of 12) into

(1) a severe group in which patients are "off their feet" before the age of 11, and

(2) a mild group in which patients are still ambulant after the age of 11.

The severe group is homogeneous and conforms to Stevenson's criteria. Inheritance is by a sex-linked recessive gene or, less probably, a sex-limited dominant gene.

The mild group is heterogeneous and may be inherited through a

sex-linked recessive gene (distinct from that of the severe form), an autosomal recessive or an autosomal dominant gene.

In the light of the above criteria, one may review some of the female cases recorded in the literature. Of the 2 female cases in Duchenne's series (1872) 1 (Case 11) started at the age of 10 with weakness in the legs and progressed very slowly, while the other (Case 13) had onset of typical clinical manifestations at the age of 4½ which progressed rapidly till the age of 6 but improved thereafter.

Gowers (1879) mentioned 3 female cases in his clinical lectures on pseudohypertrophic muscular dystrophy. One had onset of weakness in the legs at the age of 11 and fairly rapid progression so that by 15 she was unable to get up from a chair or the floor but still able to walk with difficulty. The second case was the 9-year-old sister of a boy with typical pattern of the disease but still mobile at 13. Their parents were cousins. The third case was the maternal aunt of 4 affected brothers. She had "similar symptoms and died at the age of 15."

In his large series, Erb (1891) described 4 cases of females which resemble the Duchenne type but are of slower progression. In 2 sisters (Cases 28 and 29), 12 and 11 years of age respectively, the disease commenced at 9 and progressed slowly. The other 2 (Cases 53 and 54) were sisters aged 12 and 8 who had a severely affected stepbrother aged 24 (with an unaffected father in common). Onset was in early childhood and the distribution of weakness and associated symptoms resembled the Duchenne type.

The case (Family 11) described by Sjövall (1936) with onset of weakness of the legs at the age of 3, later involving the back and shoulder girdle with inability to walk at 17 and death at 27, conforms to the "mild group" of Blyth and Pugh.

Hanhart (1949) made a further study of the large kindred previously described by Minkowski and Sidler (1928). He concluded that the disease was inherited as an autosomal recessive character. The age of onset in these cases varied from 2 to 40 years, and the rate of progression was slow. The clinical pattern conforms to the "limb-girdle" rather than the classical Duchenne type.

Of the numerous female cases with muscular dystrophy of the "lower extremity" type described by Levison (1951) there are 2 cases which conform to the "severe type" of Blyth and Pugh and, apart from being females, would also satisfy the criteria of Stevenson. In one case (Family 51) the disease started at the age of 2 and when examined at the age of 12 the child was chairbound, had gross generalized weakness (more marked proximally) and kyphoscoliosis of the vertebral column and contractures at the knees (which probably indicate that she had been chairbound for some time). In the other case (Family 75) the onset with

difficulty in walking was at $1\frac{1}{2}$ years of age and she was unable to walk by the age of 9.

Lamy and de Grouchy (1954) presented a series of 160 cases (including 11 females) of muscular dystrophy starting in the lower limbs. They concluded that 90 per cent of cases were inherited through a sex-linked recessive gene and the remainder through an autosomal recessive. They did not subdivide their cases clinically.

Kloepfer and Talley (1958) described 4 female and 3 male cases of Duchenne-type muscular dystrophy in one kindred and an isolated female case from another kindred. They concluded that the disease was inherited as an autosomal recessive trait. Their clinical descriptions conform to the "mild form" of Blyth and Pugh.

If one applies the criteria of Blyth and Pugh for subdividing the childhood forms of muscular dystrophy, the majority of the reported female cases would fall into their "mild" group. There are, however, some cases (such as those of Levison) which undoubtedly fall into the "severe" group, and inevitably some cases will be borderline between the two groups.

Case Histories

The following are detailed clinical descriptions of two sisters with progressive muscular dystrophy resembling the classical Duchenne type and apparently inherited as an autosomal recessive trait:

Case 1 (IV 15 in pedigree chart (Fig. 1)).—Age 11.

History.—Fœtal movements during pregnancy were normal. She sat up at 8 months, stood on her own at 14 months and walked at 16 months. Her gait was quite normal and she was able to skip and run. Prominence of the lateral aspect of both thighs was

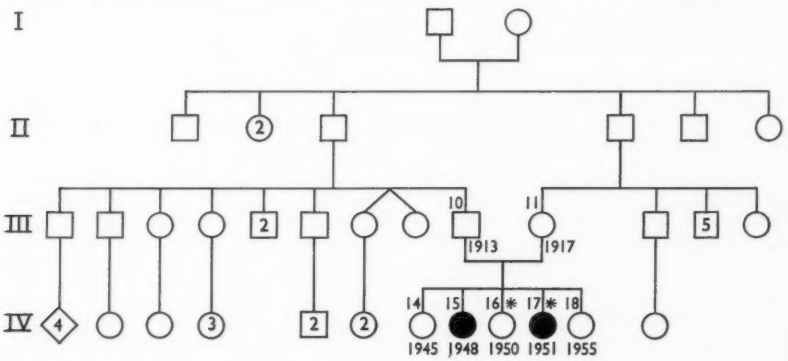

Fig. 1.

first noted by the mother at the age of 4. At 5 she began to walk on her toes and had difficulty with ascending stairs. She was unable to keep pace with her playmates at school. Her walking gradually deteriorated, she became unable to walk fast, tired readily and was unable to step on to a bus without support. From the age of 6 she fell frequently and "climbed up herself" in the characteristic dystrophic manner. She needed the help of her arms to sit up from the supine position. The mother noted prominence of the abdomen with walking. Weakness of the arms was first noted at the age of 7. The weakness of the legs and arms gradually progressed. At the age of 10 her condition was considerably aggravated by confinement to bed with influenza for three weeks. She has attended a school for physically handicapped children since the age of 7. Her intelligence is normal.

Examination.—She walked on her toes, on a wide base, with a waddling gait. There was marked lumbar lordosis. She was unable to get up from a chair or the floor and had to be helped on to her feet. She could not climb steps. There was striking prominence of the vastus lateralis muscle of both legs and, to a lesser extent, the calves and deltoids. There was marked wasting bilaterally of the medial aspect of the thigh, the glutei, infraspinatus, latissimus dorsi, rhomboids and the sternal head of the pectoralis major (figs. 2 and 3, Plate LXIX). There were no skeletal deformities and no contractures, apart from slight limitation of dorsiflexion of the ankles. The facial muscles appeared normal. The tongue was slightly enlarged. There was gross weakness of the muscles of the pelvic girdle, the trunk and the shoulder girdle (Table I). The biceps, triceps and supinator reflexes were absent, the knee and ankle jerks present but sluggish. Plantar response was normal. No abnormality was noted in other systems.

When re-examined four months later she had lost the ability to stand or walk, following on a minor injury to her knee. There was a further deterioration in her muscular power (Table I). The knee and ankle jerks were still present.

Case 2 (IV 17 in pedigree chart).—Age 8.

History.—Fœtal movements normal. Active child in neonatal period. Sat up at 8 months, stood at 12 months, walked at 16 months. She was quite normal in all her activities until the age of 6. The first abnormality noted by the mother was an apparent stiffness of the feet when putting on her shoes and difficulty in manipulating her ankles. From that time there was progressive difficulty in getting up stairs, a tendency to tire with walking, and frequent falling. She got up from the ground with great difficulty in the typical dystrophic manner. The mother also noted contractures of her toes and inversion of the feet. There was a gradual progression in the weakness of the legs. No weakness of the arms was noted. From the age of 7 she had difficulty in sitting up from a supine position without the use of her arms. She has attended a school for physically handicapped children since the age of 7. Her intelligence is normal.

Examination.—She walked with a waddling gait and a slight lumbar lordosis. Both feet had a marked pes cavus deformity with slight varus. Flexion deformities were present in all her toes at the interphalangeal joints with associated extension of the metatarsophalangeal joints (fig. 4). She climbed up herself when getting up from the floor. There was prominence bilaterally of the vastus lateralis and quadriceps muscles and, to a lesser extent, of the calves. Wasting was present in the sternal head of the pectoralis major, the medial aspect of the thighs, the rhomboids, the latissimus dorsi and the infraspinatus on both sides. Muscular weakness affected mainly the pelvic and shoulder girdles, the trunk and the neck (Table I). Apart from a restricted smile, her facial muscles appeared normal. The tongue was normal in size and movement. The biceps and knee jerks were present but sluggish, the other tendon reflexes were absent. The plantar reflex was normal. Other systems were normal.

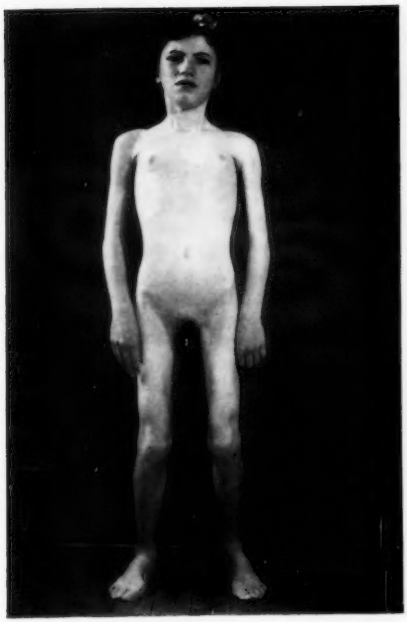

FIG. 2.

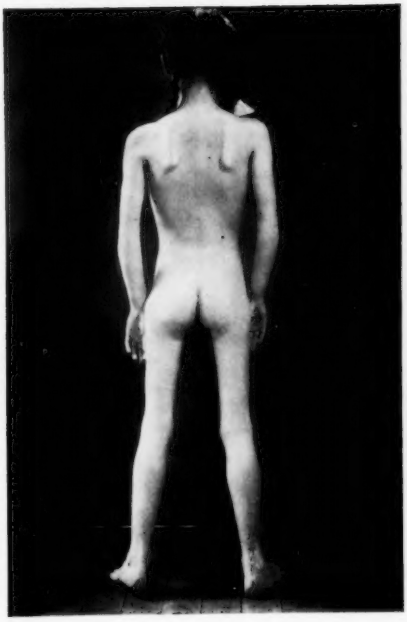

FIG. 3.

FIG. 4.

FIG. 5.

To illustrate article by Victor Dubowitz.

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TABLE I

Muscle group	Case 1				Case 2				Muscle group	Case 1				Case 2			
	R		L		R		L			R		L		R		L	
	April 1959	Aug. 1959	April	August	April	August	April	August		April	August	April	August	April	August	April	August
Neck: flexors	4	4	4	4	3	3	3	3	*Trunk:*								
extensors	4	4	4	4	4	4	4	4	extensors	2	2	2	2	4	3	4	3
sterno-mastoids	5	3	5	3	4	3	4	3	flexors	2	2	2	2	3	3	3	3
Upper extremity:									*Lower extremity:*								
Trapezius	4	3	4	3	4	3	4	3	Gluteus maximus	3	2	3	2	4	4	4	4
Rhomboids	2	2	2	2	4	2	4	2	Hip abductors	2	2	2	2	4	4	4	4
Deltoids	3	3	3	3	4	3	4	3	adductors	2	2	2	2	4	3	4	3
Shoulder flexors	3	2	3	2	4	3	4	3	flexors	3	2	3	2	4	3	4	3
extensors	3	2	3	2	4	3	4	3	extensors	2	1	2	1	4	3	4	3
int. rotators	3	3	3	3	4	3	4	3	int. rotators	3	2	3	2	4	4	4	4
ext. rotators	3	3	3	3	4	3	4	3	ext. rotators	3	2	3	2	4	4	4	4
pectorals	3	3	3	3	4	3	4	3	Knee extensors	4	4	4	4	5	4	5	4
Elbow flexors	4	3	4	3	5	4	5	4	flexors, inner	4	3	4	3	4	4	4	4
extensors	4	4	4	4	4	4	4	4	flexors, outer	4	3	4	3	4	5	4	4
pronators	5	4	5	4	4	3	4	3	Calf muscles	5	4	5	4	5	5	5	5
supinators	5	4	5	4	4	3	4	3	Tibialis anterior	5	4	5	4	5	5	5	5
Wrist extensors	5	4	5	4	5	4	5	4	Tibialis posterior	5	4	5	4	5	5	5	5
flexors	5	4	5	4	5	4	5	4	Peronei	5	4	5	4	4	5	4	5
Thumb adductors	5	5	5	5	5	5	5	5	Extensor hallucis	5	4	5	4	5	5	5	5
abductors	5	5	5	5	5	5	5	5	Flexor hallucis	5	4	5	4	5	5	5	5
extensors	5	5	5	5	5	5	5	5	Extensor digi-torum	5	4	5	4	5	5	5	5
flexors	5	5	5	5	5	5	5	5	Flexor digitorum	5	4	5	4	5	5	5	5
Fingers extensors	5	5	5	5	5	5	5	5									
flexors	5	5	5	5	5	5	5	5									
adductors	5	5	5	5	5	5	5	5									
abductors	5	5	5	5	5	5	5	5									

Key: 5 = normal power.
4 = contraction against gravity and resistance.
3 = contraction against gravity.
2 = contraction but not against gravity.
1 = flicker only.

On re-examination four months later she was no longer able to get up from the floor and there was a deterioration in her walking with more frequent falls. Several muscle groups showed a decline in their power (Table I).

A *sibling* (IV 16) aged 9 had flexion deformities of her toes and pes cavus of the feet identical to Case 2 (fig. 5). There were also flexion deformities affecting the proximal interphalangeal joints of the fingers of both hands. In both patients these deformities could be overcome by firm passive stretching.

Family history.—Examination of the parents (III 10 and III 11) and the other siblings (IV 14 and IV 18) revealed no abnormality. The father and mother are first

cousins. They are 46 and 42 respectively. There is no history of muscular disease or deformities in any other members of the family.

TABLE II

Age of onset	*No. of cases*	*Age of inability to walk*	*No. of cases*
0–2	16	0–2	1
2–3	16	2–3	1
3–4	13	3–4	1
4–5	4	4–5	0
5–6	8	5–6	0
6–7	2	6–7	0
7–8	1	7–8	9
8–9	1	8–9	10
9–10	1	9–10	14
		10–11	9
		11–12	5
		12–13	2
		13–14	1
		14–15	2

Age of 7 cases still walking: 3, 7, 7, 9, 9, 9, 15

DISCUSSION

The pattern of the disease in these 2 cases closely resembles that observed in a personal series (unpublished data) of 62 males with typical Duchenne-type dystrophy. The age of onset (first presenting symptoms) and age of inability to walk in this series are summarized in Table II. Of the 6 cases still walking at their twelfth birthday, 2 are of special interest. One case who "went off his feet" at the age of 14 has a 12-year-old affected half-brother (by the same mother but a different father) who was unable to walk after the age of 3 or 4. The other case, who went off his feet at the age of 12, has an affected younger brother who was unable to walk after the age of 8. These cases illustrate the difficulty of drawing a rigid border-line between the severe and the mild cases, assuming that siblings are affected by the same form of the disease.

Immobilization for even short periods may cause striking deterioration in muscle power in this disease. It is thus possible that some cases may prematurely lose the ability to walk as a result of confinement to bed during some general illness, or following ill-advised orthopædic intervention.

The muscular dystrophy in the two female cases described is probably inherited through an autosomal recessive mechanism. The presence of claw toes is not a feature of progressive muscular dystrophy and its occurrence in the younger case and a normal sibling probably indicates inheritance through another autosomal recessive gene, independent of that for progressive muscular dystrophy.

Conclusions

There are at least two different modes of inheritance which can produce progressive muscular dystrophy of a similar pattern in childhood. While the majority of cases of severe classical Duchenne-type are due to a sex-linked recessive gene, some are due to an autosomal recessive gene. This accounts for the occurrence of the disease in females and is probably also responsible for some of the isolated cases in males. The more benign form of the disease, with a similar clinical pattern of muscular involvement to the Duchenne-type, may also be carried by either an autosomal recessive or a sex-linked recessive gene.

There is an overlap clinically between the severe and the mild forms in childhood, and there also appears to be a gradation from the mild form in childhood to that commencing in adolescence or adult life (including the limb-girdle type).

When the fundamental nature of muscular dystrophy becomes known it may well be found that these different genes all produce a similar basic biochemical or enzymatic defect but with a slight variation in its mode or degree of expression.

Acknowledgments

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DISCRIMINATIVE RESPONSES TO STIMULATION DURING HUMAN SLEEP

BY

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Introduction

In recent years a great deal of evidence has indicated that ascending impulses, from the brain-stem reticular formation, govern the electrical signs of wakefulness or sleep that can be recorded from the cerebral cortex, and that collateral afferents from all sensory paths play an important role in exciting the reticular formation. Bremer (1954) proposed that during natural sleep the level of activity of the reticular formation could be raised by cortico-fugal impulses. In support of this, both Bremer (1954) and Brain (1958), have quoted the alleged superiority of an auditory stimulus of personal significance (such as a person's name or the cry of a child) compared with an auditory stimulus lacking special importance for the sleeper. How certain, however, is this alleged superiority? It could, for instance, be thought that any spoken name might momentarily awaken the sleeper, who then, from secondary cues, or by "scrutinizing" some immediate memory mechanism, decides that his own name has been called and so makes an overt response. The present report deals with studies designed to examine these problems.

Sensory Discrimination During Sleep

The German physiologist, Burdach (1830), wrote, "The psyche isolates itself during sleep . . . nevertheless . . . we are not always awakened by the mere sensory force of the impression, but by the psychic relation of the same; an indifferent word does not arouse the sleeper, but if called by name he awakens. . . . The mother awakens to the faintest sound from her child . . . hence the psyche differentiates sensations during sleep . . .

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we may be awakened by the lack of a sensory stimulus if it relates to the presentation of an important thing . . . the miller wakes when the mill stops." These statements won the approval of both Freud (1913) and Pavlov (1955).

Adrian (1937) said, "A loud noise which has no importance for the sleeper affects the auditory nerve as usual but produces only a transient and localized response in the cortex. The cry of a child . . . will give a message of much smaller intensity yet will set the whole brain in action." "The unfamiliar noise wakes the sleeper because the afferent message reaches the cortex and is there judged as important. The cortex signals back to the diencephalon and the rapid spread of activity ensues." Now the cry of a child is "new," or "novel," compared with the rattling of a door, the noise of the wind or the singing of the birds. Habituation, or disappearance of response on repeated stimulation is a property of stimulus-response mechanisms of all degrees of complexity (Humphrey, 1933; Oldfield, 1937). The arousal response can follow sensory stimulation during sleep. If that stimulation is repeated (as in the case of the rattling door) the arousal response would be expected to disappear even if the only sensory paths involved were collateral afferents to the reticular formation. Characteristic of habituation is the phenomenon of dishabituation—reappearance of response when a degree of novelty is introduced into the stimulus. Hence a new noise (the cry of a child) would be expected to cause arousal, even if the only sensory paths involved were collateral afferents to the reticular formation, and (contrary to Adrian's quoted remark about the "unfamiliar" noise) cortical discrimination need not be predicted as essential. Experimental confirmation of this has been provided by the work of Sharpless and Jasper (1956) who found that in cats, habituated during natural sleep to one tone, dishabituation to a new tone still occurred in cats with extensive destruction of auditory cortex, just as in normal cats. Dishabituation to a *pattern* of tones was apparently impaired, however.

Rowland (1957) has reported experiments in which cats were used, and which showed that if, for instance, a cat, in a series of waking training trials, received an electric shock after each presentation of a 25 clicks per second stimulus, then habituation of the EEG arousal reaction during sleep to that stimulus alone, was much slower than to a 240 c/sec. tone stimulus. Rowland also stated, though without reporting details, that finer discriminations, e.g. between 384 c/sec. and 480 c/sec. could be achieved.

One of the most striking features of the human sleep EEG, is the presence of K-complexes following sensory stimulation (Davis *et al.*, 1939; Roth *et al.*, 1956).

In an experiment with a human volunteer (Oswald, 1958), a conditioned emotional arousal response to the middle one of three tones, of 530, 690

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and 790 c/sec., was established. When the three tones were later presented during sleep, K-complexes to the "important" tone occurred with a much greater frequency than to the other tones, the difference being statistically significant.

Discrimination Between Names

Method

In order to eliminate the factor of novelty, subjects were given the task of responding selectively to a particular name among a steady series of names spoken while they were asleep, the degree of novelty of that particular name being no greater than that of neighbouring names.

A list was drawn up of 56 male and female Christian names and, included among these, were the names of all the students and research staff of the Institute of Experimental Psychology. A tape recording was then made, names being spoken urgently and with slightly unnatural clarity of individual syllables, in a randomised order and such that the intervals between names were 5, 7, 4, 8 and 6 seconds, repeatedly. Each name occurred singly eight times in all and then, without any break, the names were twice recorded doubly (Alan, Alan! Stephen, Stephen!. . .). There were 448 single and 112 double name stimuli.

When the recording was made, we did not know who would volunteer to be subjects. We could, therefore, hardly have spoken those subjects' names specially loudly—a possibility which is, in any case, largely provided for by the method of using control names, described below.

Each subject remained awake for the whole of the night prior to the day of the experiment, in order to ensure sleepiness. At about 7 p.m. we met, and, in some cases the subject at once received orally a 4 grain tablet of sodium hexobarbitone. Silver cup electrodes, containing electrode jelly, were then fixed to the scalp, to the palm of the left hand, and to the dorsum of the left forearm, as shown in fig. 1. The three

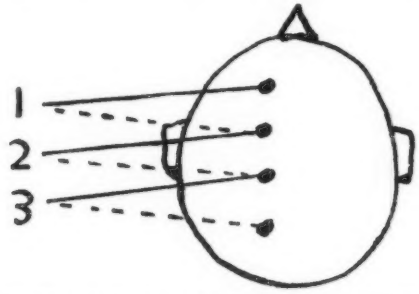

Fig. 1.—The electrode positions used in all experiments.

electrode pairs on the scalp were sufficient for the picking up of K-complexes, and the pair on the limb for recording hand movement, galvanic

skin responses (GSRs) and, usually, the electrocardiogram. The respiration was recorded in four cases, using a mercury-in-rubber tube, but this proved unsatisfactory owing to subjects turning over in sleep.

The subject was told that he was to go to sleep and that, during sleep, whenever his own name was spoken, or that of one other, control name, he was to awaken and clench his left fist. It is important to note that subjects were used as controls for each other, the "other," or control name to which each was to respond being the "own" name of one of the other subjects, the arrangement being that the "other" name, in each case, had no particular significance for the individual.

The subject then lay down, covered by a blanket, on a mattress in a small, dimly-lit room, next to the room in which the electroencephalograph was housed. About 2 feet from the subject's head was a loudspeaker which led from a Brenell Mark V tape recorder. A microphone was placed in front of the loudspeaker and connected to the electroencephalograph as a stimulus indicator (this did not give a reliable indication of the relative loudness of different stimuli, which were, in fact, fairly uniform). The EEG paper speed was generally 1·5 cm./sec., though occasionally 3 cm./sec. On the electroencephalograph available, all recordings unfortunately had to be done with a 0·03 sec. time constant.

When the subject had settled down, the tape recorder was started, the names being played at the intensity of loud conversation. The subject, in this way, grew accustomed to the constant succession of names before he fell asleep, and had opportunities to practise his responses. Some subjects fell asleep within a few minutes, others not for several hours, and three (excluded from consideration) not at all. If, after a couple of hours, the subject was still not asleep, a further 4 or 8 grains of hexobarbitone was administered orally. When the tape ended, it was rewound and played again and again in such a way that subjects slept for a major proportion of one to three playings of the tape. Each name, as it was played, was written in pencil at the bottom of the recording paper.

Assessment of Results

The EEG record of each experimental session was taken and arranged by one of us (A. T.) on a table which had been specially prepared so that the record could unfold from the right and be slid along to the left, some four feet of record being exposed, except for its bottom couple of inches, which were always covered over by a long shield. Consequently, any observer, though able to see, on the top channel, the stimulus signals (from the microphone), *could not know which names were represented*, since these were covered, and the stimulus signals themselves, as may be seen in the various figures, gave no indication of which name was involved.

The record was slid from right to left, one of us (I. O.) marking in pencil on the record the letter "N," "K" or "R" below each stimulus

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signal, according to whether, in his opinion, the particular stimulus had provoked, respectively, no EEG response, a K-complex, or some apparent lesser response undeserving of the title K-complex.

In order to merit the judgment "K," there had to be an obvious, large, slow wave and anterior 12 c/sec. waves. A mere sharp wave was not accepted as a K-complex and was called "R." The judgments "N," "R" or "K" were only made when the EEG record showed the individual to have been in sleep of suitable depth. Light sleep, characterized by low voltage 4–6 c/sec. waves, in which rather poor K-complexes could sometimes be seen, was ruthlessly excluded. Very deep sleep, characterized by high voltage 1 c/sec. waves was not scored for EEG responses either, since K-complexes cannot be seen during this. Scoring of EEG responses was thus confined to the C and D stages of sleep as defined by Loomis *et al.* (1937).

Each record was later worked through and, for each example of the person's own name, and also the "other" name, there was noted the judgment "N," "R" or "K" which had been previously written on the record, together with the judgment which had been made for the immediately preceding name.

In addition, the channel from the arm and hand was scrutinized for muscle spikes and movement artifact. Owing to the infrequency of these during sleep, it was necessary, for statistical purposes, to note, in addition to movements occurring after each crucial name, the number of movements during the period of the preceding *ten* names. The scoring of how many movements there had been, could not be done in ignorance of the names involved. Such scores are reasonably objective and any small bursts of muscle spikes, or movements, were counted.

Results

The combined results for ten subjects, one of whom had two sessions, are given below. Some excerpts which are shown are to be regarded only as illustrating the findings. Owing to occasional spontaneous awakenings, statistical treatment of results is essential.

Hand movements.—Hand movements which occurred after 131 examples of "own" name during sleep, at least as deep as the C stage of Loomis *et al.* (1937), numbered 33, and while these were predominantly large, co-ordinated responses associated with awakening (e.g. figs. 2 and 3, Plate LXX), some represented vague stirrings during sleep (e.g. figs. 4 and 5).

Hand movements to "own" name $= \frac{33}{131}$ .....(a)

Hand movements that occurred in the period of the preceding *ten* names numbered only 17, and these were mostly short bursts of small muscle spikes related to readjustments of limb position (which occur in

sleep without awakening) or other small artifacts (e.g. after "Hugh, Hugh" in fig. 5). Since there were two instances in which the sleeper awakened, in the preceding ten names, other than to one of the crucial names, and had remained awake at the time of "own" name, these are counted in equation (b) below, though they have to be excluded from equation (a) above.

Hand movements to the ten names preceding "own" name

$$= \frac{17}{1330} \quad \text{.....(b)}$$

Similarly, in the case of hand movements to the "other" name (e.g. figs. 6 and 10).

Hand movements to "other" name $= \frac{15}{124}$ .....(c)

Hand movements to the ten names preceding "other" name $= \frac{21}{1270}$ .....(d)

The differences between (a) and (b) and also between (c) and (d) are, statistically, very highly significant. In addition "own" name is significantly more often followed by movement than "other" name, for if one examines the difference between (a) and (c), $\chi^2 = 7{\cdot}1$, $n = 1$, $P < {\cdot}01$.

K-complexes.—These results are of particular importance since they throw light on the possible argument that the non-specific, noise qualities of any name might act, via collateral afferents to the reticular formation, to cause an arousal response, which might be manifest as a K-complex, and that *subsequent* to this, there might take place complex analysis of some immediate memory (the storage devices of which might be independent of the level of wakefulness). In fact, the results indicate that discriminative analysis *precedes* arousal as manifested by the K-complex.

The total number of possible K-complexes under consideration is less than the total of possible movements, since, as previously mentioned, very deep sleep must be excluded when K-complexes are considered.

K-complexes to "own" name $= \frac{73}{110}$ .....(e)

K-complexes to immediately preceding name $= \frac{37}{110}$ .....(f)

The difference between these is highly significant, $\chi^2 = 13{\cdot}4$, $n = 1$, $p < {\cdot}001$

K-complexes to "other" name $= \frac{48}{109}$ .....(g)

K-complexes to immediately preceding name $= \frac{38}{109}$ .....(h)

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The difference between (g) and (h) is not significant. "Own" name was more likely to provoke a K-complex than "other" name, the difference between (e) and (g) being statistically significant, $\chi^2 = 10{\cdot}1$, $n = 1$, $P < {\cdot}01$.

K-complexes in the absence of movement.—As would be expected, when a movement followed "own" name, there was nearly always a preceding K-complex, in fact, in 30 of the 33 instances. The other 3 cases had been scored as "R," though they could, no doubt, have been labelled "K" by a different observer, their slow wave components being small and their fast components more striking. However it was not the case that the high proportion of K-complexes to "own" name was due solely to those instances where movement also occurred, for, if the latter are excluded, we find that "own" name was still significantly more likely than the preceding name to evoke a K-complex. Furthermore, in these cases, there were not available to the scorer the occasional cues as to the name, visible in the EEG signs of full awakening that at times followed movement to "own" name.

K-complexes to "own" name when no movement $= \frac{43}{77}$ ..... (i)

K-complexes to immediately preceding name $= \frac{25}{77}$ ..... (j)

The difference between (i) and (j) is significant ($\chi^2 = 8{\cdot}5$, $n = 1$, $P < {\cdot}01$).

The onset of names spoken twice at a time.—As already described, the final part of the tape recording was made up of names spoken twice at a time. These followed the others without any break or any noticeable change of loudness. In the figures the convention of adding the mark ! after the name has been adopted to indicate that it was spoken twice. On 11 of 26 occasions this change in the pattern of repetitive stimulation caused awakening or brought about lighter sleep.

Response to Names Played Forwards and Backwards

Aim

We set out to discover whether, in a person who had been asked to "listen" to names during his sleep, such names, when recorded on tape, would be more disturbing if the tape was played in its normal direction, than if played in reverse, for the latter destroys the familiar phoneme structure and the significance of speech.

Method

The Brenell tape recorder, previously mentioned, is an instrument which can play or record upon the upper and lower tracks of magnetic tape simultaneously but quite independently.

The 56 names previously mentioned, were again spoken, to give a recorded total of 112 names, except that, on this occasion, the interval

between each name was 15 secs. The top track of the tape was used. The spools were then lifted off the tape deck and reversed, so that the track with the recorded names on it was at the bottom, and what was now the top track was clear. The tape machine was now started so that the names on the bottom track were played back in reverse at 15 second intervals. Seven to eight seconds after each of these, each name was again spoken, as before, being recorded on the top track. When this was finished we therefore had a tape on which were 224 names, half of which were recorded in one direction, alternately with the other half recorded in the opposite direction.

The tape was subsequently played in one direction to sleeping subjects, both tracks being played at as nearly the same loudness as possible. After the tape had been run in one direction, it was removed and reversed. The amplifiers for each track were now also changed over, so that if the list of names previously played forwards on the top track had had, for instance, the benefit of louder amplification, then that same list of names would have the same loudness while played backwards on the bottom track and vice versa. The tape was now played again. The output leads from both amplifiers were joined, in parallel, to the same loudspeaker.

In order to be able to compare "names forwards" with "names backwards," it was, of course, necessary that the subject should be asleep for nearly the whole time while the tape was played in both directions and that sleep should be of fairly uniform depth. Three subjects used had to be rejected because they were awake for the greater part of the second run of the tape, but seven others satisfied the requirements.

Assessment of Results

The EEG responses to the name stimuli were scored as before, except that, in addition to "N," "R" and "K," an additional category of "K+" was used to denote the more majestic, polyphasic K-complexes, the principal criterion borne in mind being the presence of three or more large slow waves in the K-complex (an example is shown in fig. 7).

TABLE I

	Forwards				*Backwards*			
Subject	N	R	K	(K+)	N	R	K	(K+)
Joan	61	30	119	(54)	132	31	47	(12)
Peter ..	128	30	36	(3)	141	24	33	(0)
Neville ..	36	24	126	(24)	85	31	69	(8)
Ian	54	16	114	(36)	99	26	57	(12)
Alex	76	49	69	(8)	104	33	60	(6)
Barrie ..	110	24	64	(2)	132	20	50	(3)
Geoffrey ..	28	24	146	(32)	56	27	114	(13)
Totals ..	493	197	674	(159)	749	192	430	(54)

In the table the scores of "K" responses include polyphasic K-complexes, the numbers of which are indicated in brackets under (K+).

Results

K-complexes.—The scores of EEG responses are shown in Table I. The small differences, with some subjects, between the numbers of backwards names and forwards names, were determined by the moments of falling asleep and waking up, for some subjects would awaken for a few seconds, or longer, several times during the playing of the tape, and scoring of EEG responses was not, of course, done for these periods.

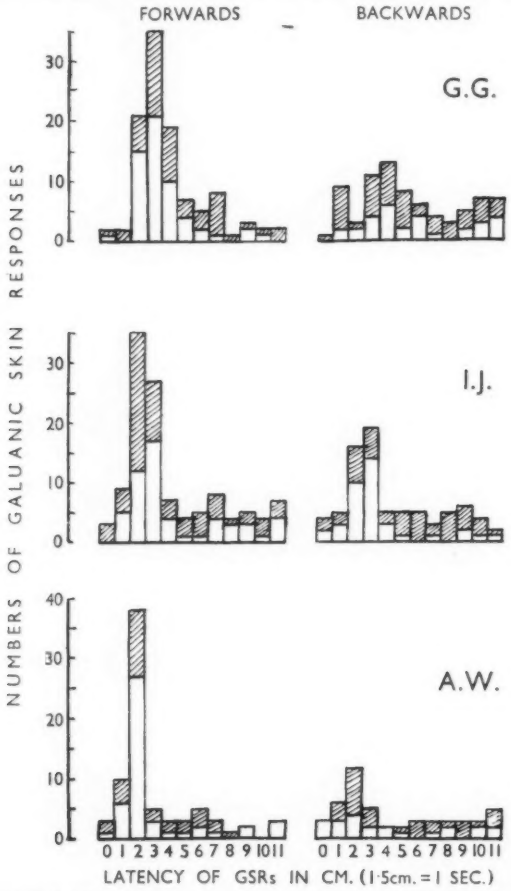
FORWARDS
BACKWARDS
G.G.
I.J.
A.W.
NUMBERS OF GALUANIC SKIN RESPONSES
0 10 20 30
0 10 20 30
0 10 20 30 40
0 1 2 3 4 5 6 7 8 9 10 11
0 1 2 3 4 5 6 7 8 9 10 11
LATENCY OF GSRs IN CM. (1·5cm. = 1 SEC.)

FIG. 8.—Three subjects showed occasional galvanic skin responses, during sleep, to the forwards and backwards names. The latency of these has been plotted in terms of centimetres of recording paper. The unhatched areas relate to the playing of the tape in one direction, the hatched areas to the playing in the other direction. It may be noted that forwards names evoked far more GSRs of 2–5 cm. latency than did backwards names.

It will be seen that names played forwards to these subjects, during sleep, were far more provocative of K-complexes than the identical stimuli played backwards, the difference being very highly significant. In addition, given that a K-complex occurred at all, it was significantly more likely to be a polyphasic one if the stimulus was a name played forwards rather than backwards. Only 54 of 430 were polyphasic, in the case of backwards names, whereas 159 of 674 were polyphasic in the case of forwards names ($\chi^2 = 20{\cdot}5$, $n = 1$, $P < {\cdot}001$).

Galvanic skin responses.—3 of the 7 subjects, at present under consideration, produced GSRs to the name stimuli. In fig. 8 are shown the distribution of GSR latency to backwards and forwards names. It will be seen that names played forwards are far more evocative of GSRs during sleep than are the same names played backwards, the difference lying in those responses having a latency period of about 1–3 secs. between the beginning of the stimulus and the beginning of the response. One of the 3 subjects produced GSRs most readily during deep sleep and, during this, obviously responded differentially to names forwards and backwards (fig. 9).

Control Studies

There appeared to be two possible factors which might have influenced the results, namely the effect of slight differences in preceding silent intervals, and the effect of the altered physical pattern of stimuli. In fact, the average silent intervals preceding the forwards and backwards names, respectively, were about the same, and a check of the results of the earlier experiments, where different intervals had been deliberately used, showed this factor to be unimportant.

A name like "Gordon" tends to be spoken in such a manner that it is louder and more abrupt at its onset than at its termination. In the extreme case a sound of very gradual onset would be relatively ineffective as a stimulus. We therefore decided to investigate this by using meaningless stimuli having such a loudness distribution.

The stimuli used consisted of alternating patterns of increasing and decreasing loudness of a 400 c/sec. tone. Each pattern had three components of equal duration, each separated by 15 decibel steps. Each component followed the preceding one instantaneously. Patterns were at seven second intervals and of 0·5 sec. total duration. Results with 2,400 stimuli, from six subjects, showed that the meaningless patterns of *increasing* loudness, far from being the less effective were, in fact, slightly but significantly the more effective in causing EEG arousal signs during sleep. Further, the frequency distributions of GSR latencies, in 4 subjects who produced these to the tone patterns, were in sharp contrast to fig. 8, there being but a small difference between increasing and decreasing patterns, with increasing patterns of loudness being slightly the more

evocative. These results with *meaningless* patterns are probably related to the fact that, when heard during wakefulness, the increasing loudness patterns appear, subjectively, greater total stimuli, being experienced as a pattern, while the decreasing loudness patterns cause an illusion in which only the first component is experienced—a manifestation of "short term auditory fatigue" (Licklider, 1951).

General Discussion

Sensory Discrimination During Sleep

It has been clearly demonstrated that sleeping subjects can make complex discriminations between repetitive auditory stimuli. They can, for instance, discriminate between meaningful words, and the identical auditory stimuli made meaningless by the reversal of direction of play of a tape recording. These latter complex stimuli apparently have little arousal effect compared with familiar and meaningful speech sounds. Language functions are commonly held to necessitate a functioning cerebral cortex.

We may suggest that, during sleep, signals from sense organs continue to reach the cerebral cortex and that the latter continues to receive, in some degree, ascending facilitation from the brain-stem: that complex analysis of the significance of the sensory signals can be made, and that, if the stimuli are personally significant, cortico-fugal signals to the brain-stem may evoke, in turn, arousal signs which may be electroencephalographic, autonomic or behavioural. Our subjects have evinced less evidence of discriminative ability in deep sleep, when the cortex presumably receives least ascending facilitation, than in sleep of medium depth. Nevertheless, some degree of that ability persists even in deep sleep (figs. 9 and 10).

Given that the discriminative analysis of the repetitive, sensory material involves cortical neurones—and the experiments of Sharpless and Jasper (1956) and Diamond and Neff (1957) support the belief that the reticular formation alone could not do this—then our suggestion of cortico-fugal impulses to the reticular formation is consistent with the beliefs of Adrian (1937) and the work of Bremer and Terzuolo (1953) and of Segundo *et al.* (1955).

We have, of course, confirmed the lay belief that a person can set himself the task of awakening to some particular stimulus and can, in fact, succeed in that task to some extent. Similarly, some people will experience more sleep disturbance than others from a given type of stimulus if they attach special significance to such stimuli, for instance, the man who is worried about his nocturnal jerks may be more easily awakened by them and so remember more of them (Oswald, 1959).

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Habituation During Sleep

Contrary to Roth *et al.* (1956), habituation of the K-complex response to recurrent auditory stimuli during sleep has been observed, being much more marked in some subjects than others.

Consideration of, for instance, fig. 3, will emphasize that the absence of some electrical response of the brain to repetitive stimulation does not imply that the principal mechanism normally underlying habituation in the mammal is a more or less peripheral blockade of sensory inflow, mediated by centrifugal fibres, as Hernández-Peón *et al.* (1957) appear to propose. Rather, failure of response may be present *after cortical analysis* of the stimulus has already established its lack of importance for the individual and vice versa. Another instance of this seemingly steady scrutiny of sensory signals, to which no obvious attention is devoted, has been provided by our colleague, Moray (1959), again using personal names.

The EEG K-complex

In Section III it has been shown that the K-complex is not only a response which appears subsequent to some analysis which has established the significance of the auditory stimulus for the individual, but that, in addition, the more significant the stimulus, the larger the K-complex. It is strange that an especially potent stimulus should evoke the most big, slow waves—which are normally the concomitant of the deepest sleep.

Summary

The work arose from the proposal that when a sensory stimulus causes arousal from sleep, cortical analysis of the personal significance of the stimulus precedes that arousal.

In order to test the belief that a person can arouse especially to his own name, it is essential to eliminate the factor of novelty of type of stimulation. Therefore a tape recording was made of 56 names, spoken urgently, at intervals of 5, 7, 4, 8 and 6 seconds, each name occurring many times in all, with also, a series of names spoken twice at a time. Sleep-deprived volunteers fell asleep while the tape was being played, having been instructed to clench their fist in response to their own and a control name.

Some subjects showed a remarkable capacity to wake up from sleep to their own name, the latter being significantly more likely to provoke a K-complex than other names, even if the subject failed to respond overtly. Ability to arouse to some other pre-selected name, though manifested, was less marked. Statistical analyses have been made of EEG responses, on the basis of ratings of the latter made in ignorance of each particular stimulus. The responsiveness largely, but not entirely, disappeared in very deep sleep characterized by high voltage 1 c/sec. waves.

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In a further series of controlled experiments it was found that personal names recorded on tape were far more likely to evoke K-complexes if played in the normal, forwards direction to a sleeping person, than were the identical stimuli played backwards. Furthermore, if a K-complex did occur, it was significantly more often a polyphasic one if the evoking name was played forwards rather than backwards. Names played forwards also evoked significantly more galvanic skin responses during sleep.

These observations are thought to indicate that prior analysis of the significance of a sensory stimulus occurs during sleep, which, owing to the complexity of the required discriminations, must presumably involve the cerebral cortex, and that subsequent arousal depends on cortico-fugal excitatory signals to the reticular formation.

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PLATE LXX

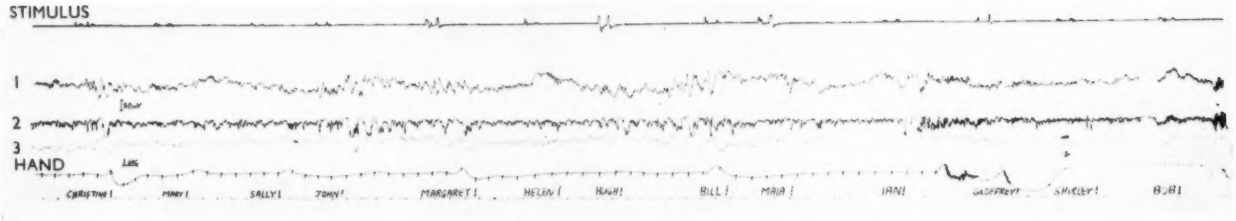

FIG. 2.

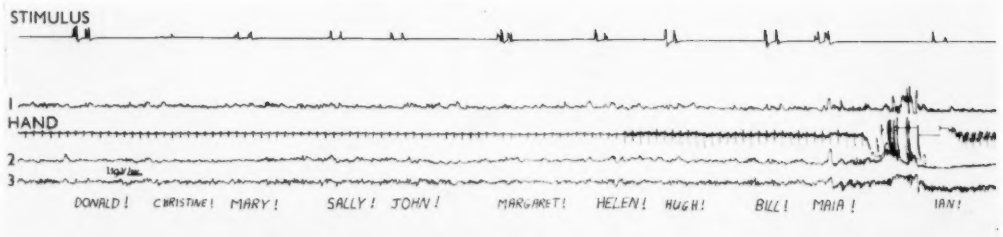

FIG. 3.

To illustrate article by Ian Oswald, Anne M. Taylor and Michel Treisman.

PLATE LXXI

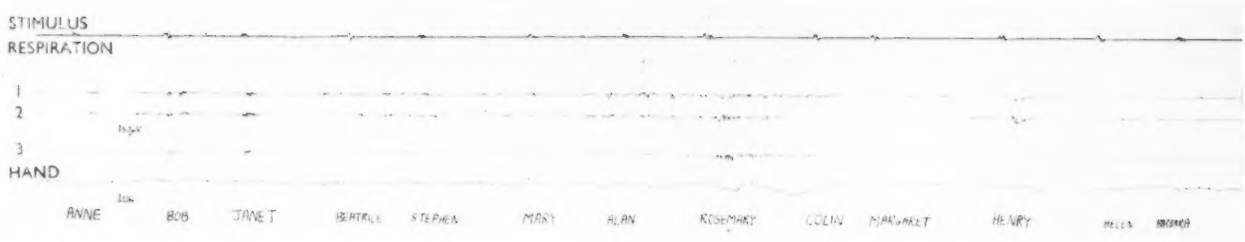

FIG. 4.

FIG. 5.

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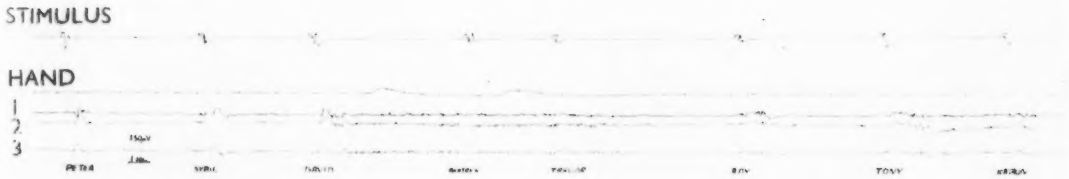

FIG. 6.

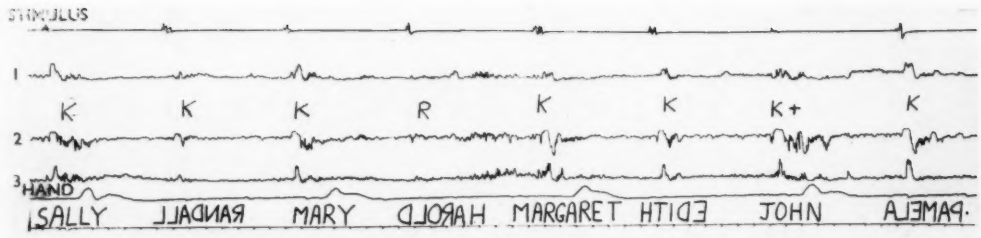

FIG. 7.

To illustrate article by Ian Oswald, Anne M. Taylor and Michel Treisman.

PLATE LXXIII

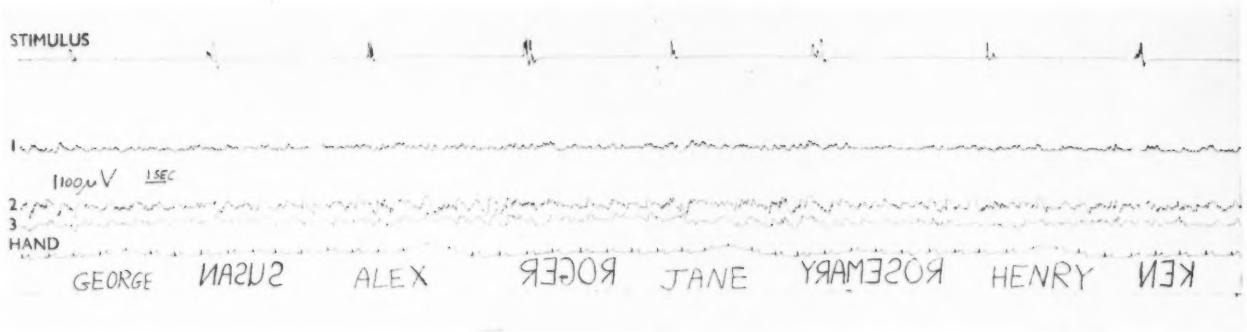

FIG. 9.

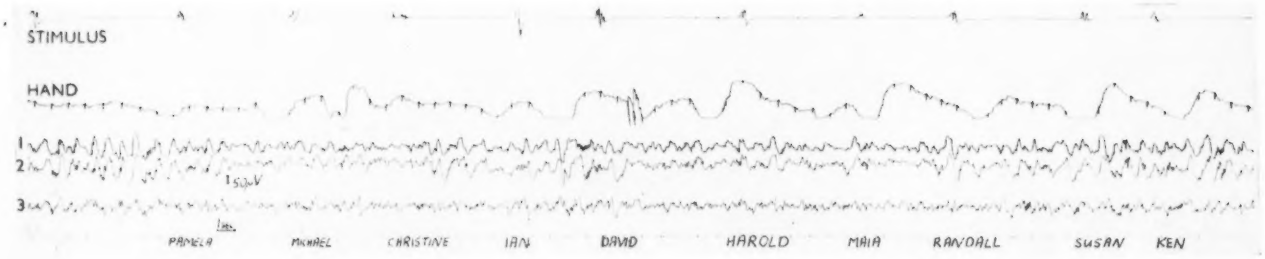

FIG. 10.

To illustrate article by Ian Oswald, Anne M. Taylor and Michel Treisman.

LEGENDS FOR PLATES

PLATE LXX

FIG. 2.—This subject's name was Ian. In the section shown the names were each being spoken twice. Though quite deeply asleep (Loomis D stage) with runs of high voltage slow waves independently of stimulation as well as K-complexes, he awakens to his own name.

FIG. 3.—This girl's name was Maia. The segment of the tape recording is the same as that in Fig. 2, but she awakes to her own name. Her record was, throughout, remarkable for the small number of K-complexes. In this section she was sleeping, with random 1–6 c/sec. waves generally and anterior spindles of faster activity, until, half a second after the first, "Maia," a large slow wave, maximal near the vertex, was seen, followed by generalized 12 c/sec. waves, then a galvanic skin response, then hand movement, then return of alpha rhythm. The amplification of the hand channel had happened to be turned up shortly before, but this was a silent event and not relevant to the awakening.

PLATE LXXI

FIG. 4.—This girl's name was Rosemary. She is in medium depth sleep, with frequent anterior spindles. She is one who showed marked habituation of K-complexes, which occur only occasionally. Her own name provokes a K-complex which stands out, and the channel from the hand, which has a base-line wobble, shows a sudden big wobble.

FIG. 5.—The same subject as Fig. 2, and the same segment of tape, in another playing through the tape, but this time only a vague movement without awakening occurred, with a lot of artifact in the hand channel. His GSRs have returned during sleep and are becoming irregular in latency. The small artifact in the hand channel after, "Hugh, Hugh" contributed to the score in equation (b) and was probably caused by pulling on leads due to a deep respiration associated with the large, polyphasic K-complex.

PLATE LXXII

FIG. 6.—The same subject as Fig. 5 (different session). He has been asked to respond not only to his own name but also to David, which causes brief arousal and a hand squeeze (just visible during the second half of the GSR).

FIG. 7.—An example of the scoring of the EEG responses in terms of K and K+. The GSRs which follow names played forwards may also be noted (Subject G. G. of Fig. 8).

PLATE LXXIII

FIG. 9.—To illustrate the depth of sleep in which this man, subject A. W. of Fig. 8 showed, by his GSRs, discrimination between names played forwards and backwards. He was here, of course, too deeply asleep for K-complexes to appear and his record is dominated by $\frac{1}{2}$-2 c/sec. waves with some faster spindles (Loomis D stage). His personal EEG sleep record was of rather lower than usual voltage and the fact that, as mentioned in the text, a time-constant of 0·03 sec. had to be used, should be borne in mind. His deepest sleep occurred between the 60 and 112th names of the first playing of the tape and in this period there were 30 GSRs of 2·5 cm. latency (1·5 cm. =1 sec.) to forward names, compared with 6 to backwards names. When the tape was reversed the same particular length of tape now evoked 12 GSRs of the same latency to forwards names and only 8 to the names which were now backwards, showing that loudness could not be responsible for the difference illustrated.

FIG. 10.—The subject is very deeply asleep with high voltage 1 c/sec. waves in his EEG and the swinging changes of palmar skin potential which sometimes occur in very deep sleep. He has failed to respond to the last four of the names to which he was supposed to respond—Ian and David. There has been no movement artifact for sixteen minutes. Now Ian and David come together and movement artifact is visible. No more movement occurred till ten minutes later, when the double names began.

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THE CEREBROSPINAL FLUID VALVES

BY

KEASLEY WELCH AND VERNER FRIEDMAN[1]

JUST before the turn of the century, while working in the Hallerianum in Bern under the supervision of Kronecker and Kocher, Harvey Cushing conceived that there might be valved openings between the meninges and the venous channels of the dura. By permitting the flow of whole cerebrospinal fluid into the venous system while preventing escape of blood in the reverse direction, such valves would meet the simple requirements of a drainage system for meningeal fluid and would place its circulation in a situation analogous to that of lymph.

In the Mütter Lecture for 1901 Cushing spoke about his surmise, "Whatever the nature of these openings may be, or wherever their situation, they certainly are of considerable size and apparently possess a valvular action. The process is not a mere filtration through a membrane. This is readily shown experimentally by the fact that an injection mass entered, for example, in the lumbar meninges, may be easily made to pass from the cerebrospinal space into the longitudinal sinus, and thence through the jugulars into the right heart. An injection in the opposite direction by way of the veins never, or but exceptionally and in small amounts, gets into the cerebrospinal space.

"The freedom of the communication of the subdural space with the sinus is demonstrated, furthermore, by the substances which will pass from one to the other. If, as occasionally happened during my experiments with local compression, the rubber pressure-bag containing mercury should rupture, and the globules of quicksilver enter the subdural space, they will be found distributed in the sinus, the jugulars, in the right heart, and throughout the lungs" (Cushing, 1902).

During the next thirteen years he was to hold this viewpoint and it was to colour the studies of cerebrospinal fluid drainage which were launched in Baltimore and carried out later in Boston. These, undertaken by Weed, finally led Cushing to abandon his idea. Weed studied serial

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sections of the sagittal sinus without finding any valves. Moreover, his classic experiment, based upon the finding of Prussian blue granules in the arachnoid villi and sinus after subarachnoid injection of iron ammonium citrate and potassium ferrocyanide, and the subsequent acid fixation of the head, was interpreted to demonstrate that the meningeal fluid passed into the blood by a process of filtration through the arachnoid villi (Weed, 1914).

In the introduction which he wrote to the papers on cerebrospinal fluid from the Laboratory of Surgical Research at Harvard, Cushing admitted, "Weed's studies of the arachnoid villi have effectively exploded my preconceived ideas in regard to the escape of the fluid by valvular action and have brought us back to the view of seepage through the arachnoid projections into the dura as the chief manner of fluid outflow" (Cushing, 1914). It is not possible to read this article, however, without feeling that this recantation lacked enthusiasm and that, even as he wrote, he regarded his "preconceived ideas" with some tenderness. Be that as it may, the cerebrospinal fluid valves were put aside and were not even mentioned in the Cameron Lecture, *The Third Circulation* (Cushing, 1926). Since, they have been treated as hardly more than material for a brief anecdote in the history of thought on the problem (Wislocki, 1932; Weed, 1938).

The anecdote does emphasize the difficulty which still persists in reconciling the behaviour of cerebrospinal fluid outflow with its structural basis. The mechanism for transfer of cerebrospinal fluid into the blood suggests an open flow valved arrangement. If it be remembered that there is imposed a resistance equivalent to 50 mm. of water (this being the difference of pressure between fluid and sinus blood) we might substitute for the "considerable size" envisioned by Cushing a calibre of approximately capillary proportions.

Anatomy of the Arachnoid Villi

While it remains widely believed that the arachnoid villi are concerned with the drainage of cerebrospinal fluid, the evidence for this is not as strong as was formerly thought. It is understood that the Prussian blue experiment does not define the drainage route (Sweet *et al.*, 1954) and it is recognized that Weed's observations were, in some important particulars, incomplete (Scholz and Ralston, 1939; Howarth and Cooper, 1955). That their role relates to reabsorption of fluid is suggested by their disposition which brings the fluid into close relation to the venous blood.

Although differing in their treatment of such details as the coverings of the villus, descriptions are in agreement that the essential structure is a blind diverticulum of the arachnoid into a venous channel (Weed, 1914; Clark, 1920; Schaltenbrand, 1955; Turner, 1958). With these descriptions our own observations do not agree. Instead it will be shown that a villus

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is a labyrinth of coapted tubes which connect, from place to place, with each other and which open to the subarachnoid and subdural spaces on the one hand and to the venous channels of the dura on the other. The structure is so delicate that should the pressure surrounding it exceed that within, the villus will be collapsed, the tubes effaced and a passageway will no longer exist. Thus it forms the structural basis for a valved canalicular system allowing the passage of whole cerebrospinal fluid into the blood.

Method

The anatomical studies reported here were made on tissue of the African green monkey (*Cercopithecus athiops sabæus*). Formalin fixation, paraffin embedding and serial sectioning were carried out. Only those villi related to the superior sagittal sinus were examined. The studies were based upon tissue removed from 12 animals but a great number of the conclusions are based upon a particularly favourable series of sections from one animal. Where special methods were employed they are described in appropriate portions of the text.

Observations

Location and relations.—In the monkey, as in human subjects, portions of the internal aspect of the dura mater near the sagittal sinus have a textured rather than a smooth surface (fig. 1, Plate LXXIV). In the monkey this is seen most regularly in the neighbourhood of the entrance into the sinus of the parieto-occipital vein. Here, the innermost interlacing fibres of the dura form pillars at the mouths of hollows. Into some, but by no means all, tubes of arachnoid lead (fig. 3). Many, in the young monkey, are in communication with the subdural space.

Some of the hollows are simply blind pouches into the dura, but from the bottom of others, the arachnoid villi take origin. They project into, form septæ in, and form parts of the walls of the lacunæ laterales (fig. 2).

General features.—The arachnoid villi in the young monkey are made up of a number of tubes, the walls of which are shared with adjacent tubes so that the appearance on cross section is almost that of a glomerulus (figs. 4, 5 and 6). In what may arbitrarily be taken as an average condition, the tubes vary in diameter from approximately 4–12 microns. The cells which make up the structure contain round or oval nuclei. Surrounding the nucleus is a rather sparse amount of cytoplasm which is sometimes granular. As the cytoplasm extends away from the nucleus it becomes flattened to form the delicate tubular wall. There appear to be fibres supporting the wall as well. The tubes communicate with adjacent ones from place to place so that the arrangement could be well characterized as a maze.

The surface in the young animals is, in most places, not very different from the tubular walls within, being made up of flattened mesothelial cells. In some places these are piled up into a number of layers but "cell caps" are also sometimes encountered in the depths of the villus

(figs. 3 and 4). These aggregations of cells are to be distinguished from a collapsed portion of a villus which has a superficially similar appearance only. From the surface, invaginations extend deeply into the structure and in a single section, unless the surface opening is in the same plane, such a pit is not distinguishable from a tube intrinsic to the villus. Here and there the latter communicate with the former by narrow openings in their common wall, the border of these sites of communication being frequently marked by small collagen deposits. Thus, the tubes intrinsic to the villi are in open if circuitous communication with the lumina of the lacunæ laterales. The tubes at the base of a villus tend in general to be larger than those near its surface and occasionally one of these basal tubes connects one tuft with another. Just as in serial sections it is possible to demonstrate communications between the tubes of the villi and the lacunæ laterales, it is also possible to show openings between these basal tubes and the subarachnoid and subdural spaces.

Especially in the case of those villi which form septæ in the lacunæ, coronal sections will frequently reveal the tubes in their long axes. There are occasional lymphocytic aggregates in the dura, spreading into and occupying the tubes of a villus.

Changes in appearance with changed pressure relationships.—When the villi are fixed by arterial or venous perfusion during a condition of reduced cerebrospinal fluid pressure, brought about by cisternal drainage, their appearance is quite different from that described. They are collapsed. A tubular structure can barely be discerned if at all. In this condition the cells of the villus become rounded as they are less flattened so that the effacement of the tubes depends, not only upon the reduction of their diameter, but upon the bulging of the lining cells into the lumina as well (figs. 7 and 8).

On the other hand when the villi are fixed by perfusion of formalin into the subarachnoid space (under pressures considerably greater than physiological) they are seen to be greatly distended and deformed (figs. 9 and 10). The cytoplasm of the cells of the villus is greatly attenuated and some of the tubes are actually ruptured.

An attempt to demonstrate the architecture usual in life.—It is clear that a structure, the architecture of which changes so readily in response to pressure differences must have an average or usual condition during life. In an attempt to learn what this might be, a monkey was anæsthetized and the upper portion of the cavalrium removed. The animal's head was then immersed in liquid nitrogen and, in the frozen condition, blocks were cut and treated in several ways. On frozen section the nuclear pattern in the villi could be well seen but the cytoplasm could not be well stained. In frozen, dehydrated, paraffin imbedded tissue which was unfixed, rather poor histological preparations were obtained, but

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these revealed an architecture indicating an open, but not distended villus (fig. 11).

It is of interest that these preparations give some support to the contention of Winkelman and Fay (1930) that the lacunæ laterales ordinarily contain cerebrospinal fluid rather than blood. This point, which will require further study, is suggested by the fact that a clearer fluid than blood was identified in the lacunæ in this frozen material.

Comment.—The idea that the appearance of arachnoid villi might vary in response to hydrostatic pressure differences in the meninges is an old one. Le Gros Clark (1920) reviewed the evidence for the long-held belief that the Pacchionian bodies are more numerous and larger in situations where cerebrospinal fluid pressure is increased. He considered those bodies to be distended arachnoid villi. Key and Retzius (1876) characterized the Pacchionian granulations as erectile under the conditions of their experiments which involved the injection of gelatin under high pressure into the subarachnoid space. Thus, it has been clearly recognized for many years that the pressure within an arachnoid villus is a reflection of that of the cerebrospinal fluid while the pressure surrounding the villus is that of a part of the venous system in which it lies. It is fair to say, however, that the significance of the distension and collapse in providing a valvular action has not been appreciated because it has not been realized that there are openings between the interior and the exterior. This is not to say that evidence for such openings has not existed. It is to be found in the experiments of Key and Retzius in the passage of gelatin solution out of the Pacchionian bodies into the sinus. It was in fact, this very point that was seized by Weed (1914), who held it as evidence of artifact, to discredit the validity of the experiment. More recently Hoffman and Thiel (1956) upon observing the passage of injected carbon particles past the villi into the venous system, considered this to be due to rupture of the cell caps of the villi and not therefore related to the capacity of normal villi to pass such particles.

The deductions which can be made from a study of the structure of the arachnoid villi under varying conditions are that these provide open communications from the meninges to the venous system when the pressure of the cerebrospinal fluid sufficiently exceeds that in the venous sinus and that the passages are closed when the pressure relations are reversed (fig. 12).

In the next section the various experiments designed to test this hypothesis will be described.

Factors Governing Flow Through the Cerebrospinal Fluid Valves

Fortunately, the disposition of the arachnoid villi is such that their functional capacity can be studied in excised preparations. By arranging

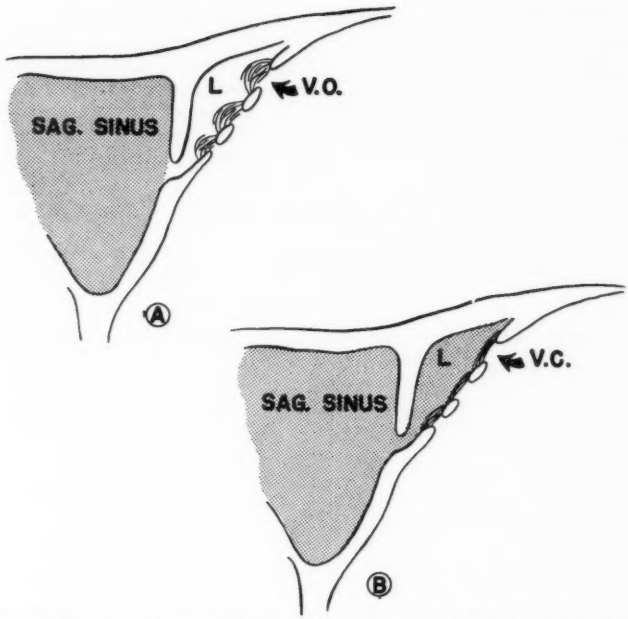

FIG. 12.—Diagrammatic illustration of the situation and function of the arachnoid villi. When the meningeal pressure is sufficiently greater than that in the sinus the villus mazework is open as in (A). When the meningeal pressure is below that in the sinus, reflux of blood is prevented by collapse of the villus (B).

a portion of dura which bears villi as an occluding membrane between two tubes, the relation between pressure and flow has been examined.

An experiment based upon a somewhat similar idea was carried out long ago by Leonard Hill (1896) using basal portions of canine and human dura mater. He described flow from the internal to the external surface.

For the special parts of the dura bordering the superior longitudinal sinus, unidirectional flow from the internal surface to the sinus was observed in the experiments to be described.

Method

The experiments were made with tissue obtained from African Green Monkeys shortly after death. Ovum forceps were modified so that into each ring there was fitted a specially fashioned polyethylene tube. One of the tubes was securely fastened in its ring. The other was loosely placed so that a small amount of play was allowed. This loose fitting, together with the elasticity of the metal in the long handles of the forceps, ensured that upon closure, a ridge on the opposing face of one tube would always be engaged in a groove on the opposing face of the other. A disc of dura could thus be held as an occluding membrane between the tubes.

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After a craniectomy was made under anæsthesia, the animal was killed by exsanguination, and then held erect so that blood might drain away from the head. The superior sagittal sinus was opened in the mid-line and the convexity dura cut on each side so that it was hinged upon the sinus. The tubes were applied in such a way that the sinus was open to the one side and the internal surface of the dura was exposed to the other (fig. 13). The application was ordinarily made in the neighbourhood of the parieto-occipital vein where the tissue is rich in arachnoid granulations.

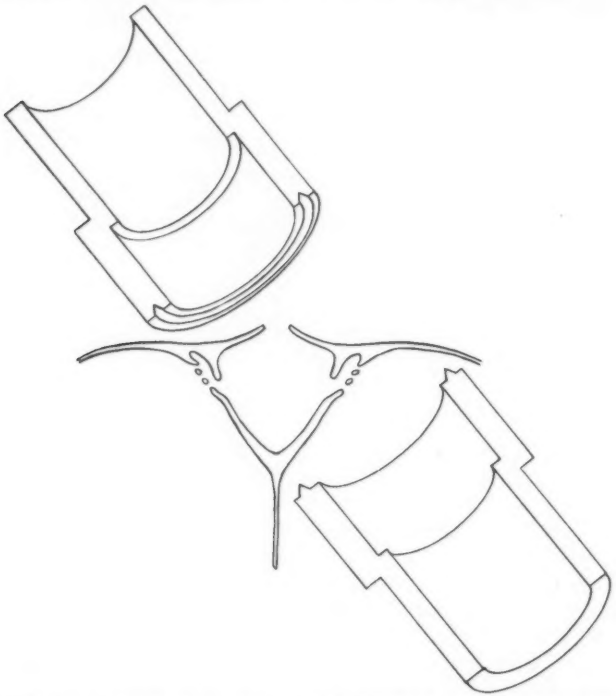

FIG. 13.—Diagrammatic representation of the application of the tubes to the dura mater. When the tubes are engaged, a disc of dura is held as an occluding membrane between them.

After the forceps were engaged, the specimen was cut free from the remaining dura. One or other side was attached to a reservoir containing Ringer lactate solution, the other to a small calibrated polyethylene tube, and flow was measured by movement of a bubble.

After the experiment, the disc of dura was removed and serially sectioned for histological study.

Difficulties, precautions and controls.—Should the dural disc include a segment of a superior cortical vein which is cut or broken at a distance from the sinus, this will act as a flutter valve allowing passage of perfusion fluid from the sinus side to the meningeal side. A similar pressure-flow relation can exist if the falx is cut across and its cut edge is exposed to the meningeal side, or if the bite of the opposing tubes on the

falx becomes loose and a cut edge of falx is exposed. If a vein is avulsed from the sinus, and the place of its entrance is included in the occluding disc, flow can proceed in both directions through this hole. In a few experiments holes have appeared in the disc, apparently due to the trauma of the manipulations involved in arranging the experiment.

A number of discs of convexity dura have been tested, and a minimal flow at high pressure in each direction has been the rule.

The Relation Between Pressure and Flow

The definiteness of valvular behaviour.—The more detailed analyses of the flow-pressure relations which will follow, reveal nothing of greater significance than this, that flow is essentially unidirectional from the meningeal to the sinus side of the membrane (figs. 14, 15, 16 and 17). The

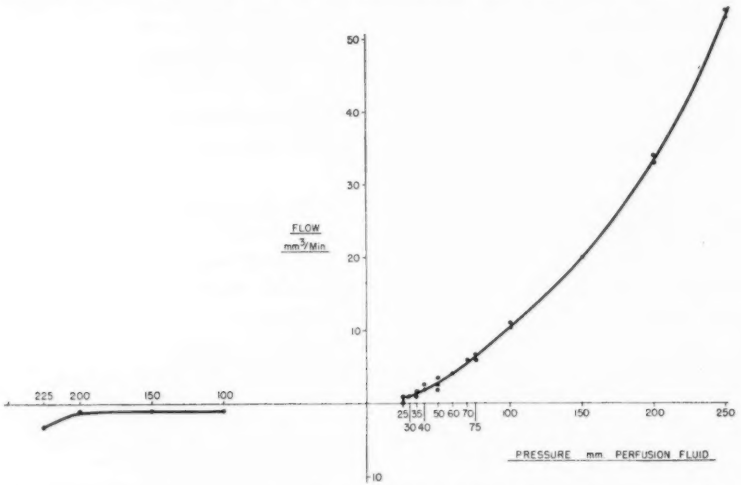

FIG. 14.—Flow-pressure curve through a dural disc, illustrating essentially unidirectional flow from the meningeal to the sinus side of the disc. The pressure difference across the disc is represented to the right of the vertical axis when the pressure is greater on the meningeal side and to the left when the pressure is greater on the sinus side. The critical opening pressure is just below 25 mm. of perfusion fluid.

measured flow from the sinus to the meningeal side occurs at relatively high pressure and is comparable in degree to that seen through convexity dura.

The general structure of the flow-pressure curve.—The curve meets the pressure axis at a value which is usually between 20 and 50 mm. of perfusion fluid. This value is the critical opening pressure of the valves. Just above the critical opening pressure the curve is frequently concave to the pressure axis and there follows a long segment which usually includes all

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measured values of pressure after the initial concavity is overcome in which the curve is gently convex to the pressure axis. Occasionally the curve bends again at high pressure so a second concavity presents to the pressure axis.

Some of the curves have remained stable over the period of hours during which they have been studied. Others have remained stable for a time and have then drifted, either abruptly or progressively so that, although the critical opening pressure was little if at all affected at first, the flows at values above this level were increased. Later the critical opening pressure was reduced.

The critical opening pressure.—The critical opening pressure is defined as that pressure at which perceptible flow begins. It is the pressure required to open the tubes of the valves and to hold them open against a tension which tends toward their collapse. The latter tension is, of course, present at all values of pressure and flow. Thus, at values of pressure at which flow occurs, a pressure equivalent to the critical opening pressure is

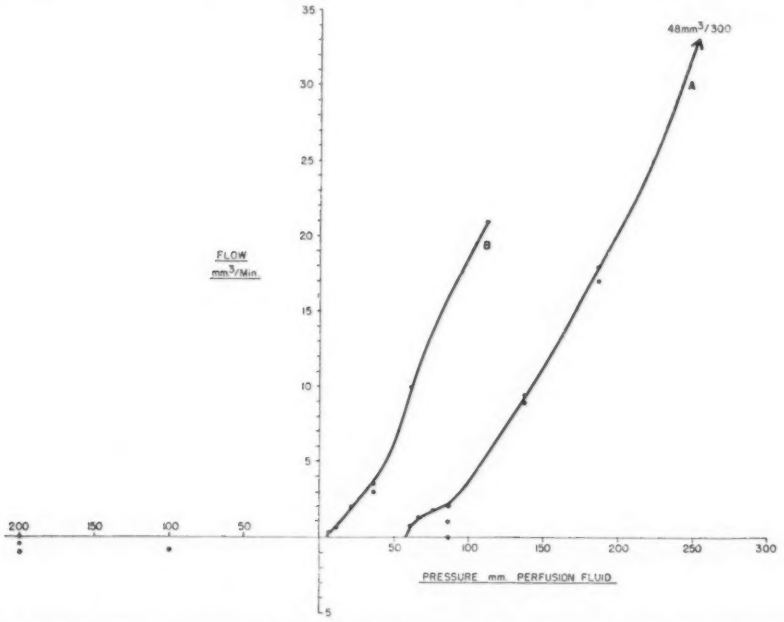

FIG. 15.—Flow-pressure curves through a dural disc bearing arachnoid villi. Curve (A) represents the flow-pressure relationship for the perfusion fluid. Curve (B) was obtained after the addition of Tween 80 to a concentration of 1/2,000 in the perfusion fluid. The critical opening pressure, which was in the neighbourhood of 60 mm. of perfusion fluid was virtually eliminated by the wetting agent.

maintained even at the distal ends of the tubes and is not available for perfusion.

These considerations are analogous to those which have been raised in relation to the perfusion of blood vessels. Closure of small blood vessels has been shown to occur at a positive critical pressure (Burton, 1951; Nichol *et al.*, 1951; Doyle, 1953). In that the residual closing tension, after vasomotor tone was abolished, could be eliminated by the addition of a wetting agent to the perfusate, it was considered to be based upon the interfacial tension between the perfusion fluid and the partially unwettable vessel wall (Nichol *et al.*, 1951).

Analysis of the closing tension of the cerebrospinal fluid valves reveals it to be similar to the residual critical closing pressure of blood vessels in that it can be reduced by the addition of a wetting agent to the perfusion fluid. Fig. 15 illustrates an experiment in which the flow-pressure curve was determined and then a wetting agent (Tween 80) was added to the perfusion fluid. The whole curve was moved to the left, the critical opening pressure virtually abolished. It is interesting that in the low pressure range, the elimination of the closing tension resulted in a very great increase in flow.

The initial segment.—At pressures just higher than the critical opening pressure the slope of the curve is frequently concave to the pressure axis. The slope of the initial portion of the curve is frequently greater than that which is to follow until relatively high pressures are reached. This could be due either to the opening up of additional villi as their critical opening pressures are exceeded or to a situation in which the walls of some of the tubes which are opened are still slack and are not yet exerting an elastic tension.

The elastic phase.—After the initial rise most of the curves were convex to the pressure axis indicating, over the range measured, an elastic deformation of the walls of the tubes. In this connexion the experiments of Mortensen and Weed (1934) must be mentioned. They perfused the subarachnoid space of living dogs under carefully controlled conditions and measured the relation between the external pressure and the rate of flow of fluid into the meningeal spaces. The relation between pressure and flow was not a linear one as might have been expected on the basis of Weed's theory of cerebrospinal fluid drainage. Instead, the slopes of the curves increased as the pressure was increased. Thus, their results as well as our own, however incompatible with existing theory, are explicable on the basis of a mechanism of open drainage through elastic tubes.

Internal derangement at high pressures.—In a few experiments the curves have bent, at high pressure, so that they presented a second concavity to the pressure axis (fig. 16). At these high pressures in other words, there has been the equivalent of a narrowing of the tubes or apertures with

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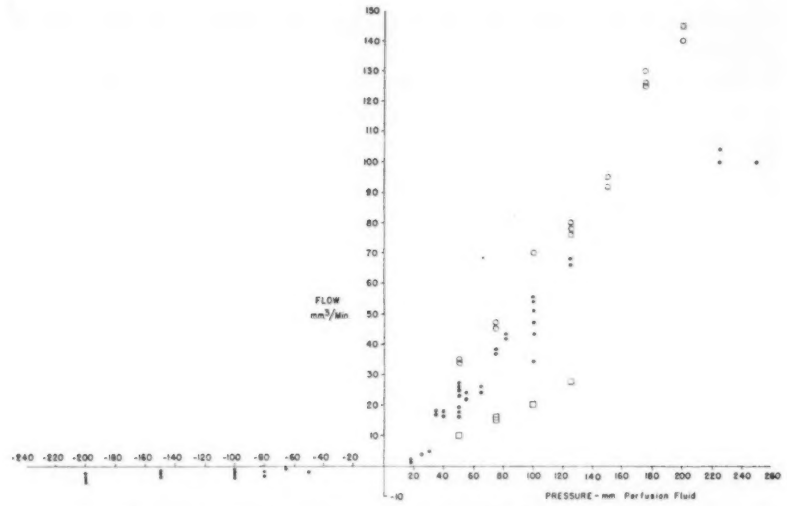

FIG. 16.—The values of flow and pressure represented by the squares were recorded in the earliest part of the experiment. Those indicated by the dots were obtained later. The flow-pressure curve outlined by the dots can be seen, at high pressure, to present a concavity to the pressure axis. The values represented by the open circles were obtained last.

increase in pressure, an internal derangement of the valve. A structural basis for this derangement is suggested in some of the histological preparations made when the villi were fixed under conditions of high meningeal pressure. Figs. 9 and 10 demonstrate two examples of a mechanism by which dilation of part of the valve might impinge upon parts more distal leading to an effective narrowing of the openings. In one instance, some of the tubes in the central part of a villus have dilated at the expense of neighbouring tubes which are collapsed. In the other an entire villus is greatly distended in such a way that an aperture is narrowed and elongated.

The drift of the flow-pressure curve.—Some of the flow-pressure curves have shown progressive drift to the left and upward. The earlier changes affect the upper portions of the curve and apparently reflect changes in elasticity. Later, the critical opening pressure is affected and the limit of drift seems to be a straight line going through the origin. It is known that after death, endothelial cells become completely wettable and it seems reasonable that the drift is due to changes both in elasticity and in wettability associated with death of the specimen.

The colloid osmotic pressure of the blood.—The evidence that the colloid osmotic pressure of the blood influences the drainage of cerebrospinal

fluid is, to say the least, tenuous. It is based upon the observation by Weed (1935) that gelatin, serum protein, and casein solutions pass less rapidly than does saline from a reservoir into the subarachnoid space. Weed's interpretation, that the loss of part of the osmotic component of the pressure difference between meninges and sinus blood accounted for the slowing, is not the only explanation available. It has been criticized by Davson (1956) who points out that the protein would tend to draw fluid to the meninges from the brain and thus increase the effective volume administered.

That the drainage of cerebrospinal fluid is an open one does not in itself dispel the possibility that the colloid osmotic pressure of the blood might play a part. Were the villi bathed in blood, and there is some evidence that they are not, and were the walls of the tubes and coverings to behave as a semi-permeable membrane, there might be combined an open flow system through the lumina of the tubes and a diffusion through their walls.

This problem has been approached in two ways. First, after recording the flow-pressure characteristics of a specimen, blood serum has been placed on the sinus side of the occluding dural membrane. Were both

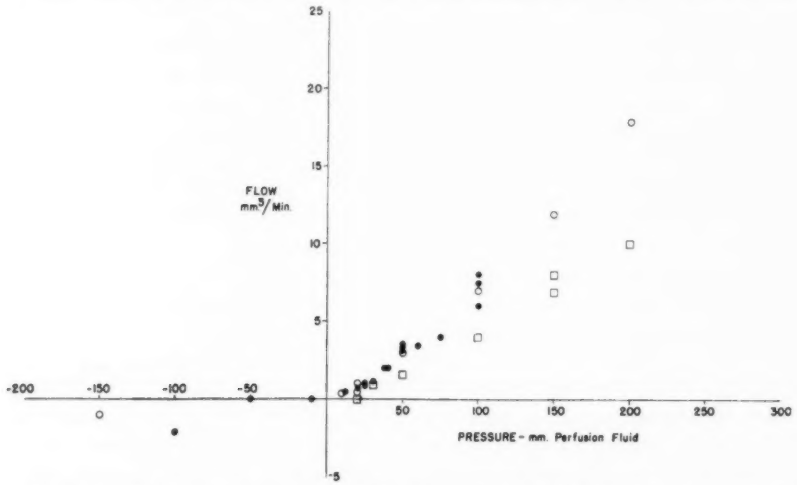

FIG. 17.—The values of pressure and flow represented by the closed circles are those obtained when the entire system contained Ringer-lactate solution. Those represented by the open circles were measured when the sinus side of the occluding membrane was bathed in blood serum. No effect of the colloid osmotic pressure of the serum was observed. The values represented by the squares are those recorded when blood serum was employed as the perfusate. The reduction in flow of blood serum, as compared to that of Ringer-lactate solution, is approximately that expected on the basis of its viscosity.

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hydrostatic and osmotic forces effective in determining the pressure difference, an accelerated flow would be expected. No such effect upon the flow of perfusion fluid has been measured. Second, the flow of blood serum placed on the meningeal side has been measured and compared to that of non-protein perfusion fluid. In this situation the reduction in the rate of flow of serum as compared to that of perfusion fluid is explicable on the basis of its relative viscosity (fig. 17).

Therefore, evidence for an osmotic effect upon flow has not been obtained.

The significance of the perfusion curves.—The curves confirm, in a general way, the predictions made as a result of the anatomical study. They show that a valvular mechanism is indeed operating under the condition of the experiment. At the same time they reveal more than could be surmised, from morphological considerations alone, about the conditions which govern flow from the meninges into the venous system.

The method isolates for individual study and consideration, the mechanism which is considered to be the principal one for drainage of cerebrospinal fluid. In the intact animal where the exchange of constituents between fluid and blood is continuous, it is difficult to achieve this separation.

On the other hand the experimental situation is an artificial one. The perfusion fluid used does not have the same rheological characteristics as cerebrospinal fluid. Its viscosity and surface tension are certainly different from those of lumbar fluid and it is not at all certain that the properties of the latter are the same as those of the fluid entering the villi. Moreover, the experiments have been carried out on dying specimens, the characteristics of which have often changed during an experiment.

Perfusion experiments designed to measure the rates of passage of particles of various sizes through the arachnoid villi are being undertaken and will be reported separately.

Discussion

A great deal of the evidence which relates to the behaviour of the drainage of cerebrospinal fluid is in keeping with an open flow, valved system such as Cushing proposed. First, there is the everyday experience that reducing the cerebrospinal fluid pressure by withdrawing fluid does not result in meningeal hæmorrhage. Weed (1914) actually made formal by experiment the corollary observation that temporarily elevating the venous sinus pressure over that in the subarachnoid space does not result in reflux of blood into meninges. Not only whole blood but also its unformed constituents fail to pass backward along the route of drainage. Analyses of fluids, obtained under conditions of constant drainage over a

wide range of pressures, show unvarying concentrations of their components (Bering, 1958).

It is known, however, that proteins pass quite readily out of the subarachnoid space (Courtice and Simmonds, 1951; Sweet and Locksley, 1953). Courtice and Simmonds showed by analysing the cervical lymph and blood after subarachnoid instillation of dye-labelled protein in cats and rabbits, that most of the protein passes directly into the blood. Sweet and Locksley proposed that the function of the arachnoid villi and therefore of the drainage mechanism, relates to the removal of cerebrospinal fluid protein. Sweet (1957) has compared the cerebrospinal fluid flow to that of lymph and has cited the arachnoid villi as acting "in lieu of valves." Red blood cells also pass out of the subarachnoid space and into the blood but at a slower rate (Simmonds, 1953), and, that their absorption was uninfluenced by ligation of cervical lymphatics suggested that they too may pass through the arachnoid granulations.

It looks very much then as though the arachnoid villi prevent the constituents of blood from passing into the meninges but allow the passage of these very constituents from meninges into the blood. Although other explanations have been offered (Davson, 1956), the simplest is that the passageway is a valved one. To this more or less indirect evidence must be added the direct evidence offered above. The contention that there is open flow through the arachnoid villi could best be supported by direct observation during the passage of materials through the villi, an objective which has not yet been achieved. However, there is offered a histological demonstration of an open passage. The existence of a valved arrangement is suggested by the change of structure of the arachnoid villi in response to pressure changes, and demonstrated by the perfusion experiments.

Summary and Conclusions

The traditional concept that an arachnoid villus is a blind diverticulum of arachnoid into a venous channel, and that it serves as a membrane through which cerebrospinal fluid passes into the blood, has been reexamined by experiments in monkeys.

An arachnoid villus, it has been learned, is a labyrinth of small tubes which establish open connexion between the meninges and the venous blood. In that these tubes are opened by the pressure of the cerebrospinal fluid when this is sufficiently greater than that of the blood, and effaced when the pressure relation is reversed, the structure is, in fact, a valve.

Fortunately, the peculiar anatomical disposition of these valves permits that they be perfused in excised preparations. Flow-pressure studies confirm that flow is essentially unidirectional through elastic tubes above a critical pressure which is based upon interfacial tension. No influence of colloid osmotic pressure upon flow is detectable.

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LEGENDS FOR PLATES

PLATE LXXIV

FIG. 1.—A portion of the internal surface of the dura mater near the junction of the parieto-occipital vein with the sinus is portrayed. The intertexture of dural fibres gives the dura a woven appearance. The meshes, between the interlacing filaments of dura, are shallow recesses, and it is at the depth of these that the arachnoid villi are attached. Magnified approximately ten times.

FIG. 2.—A low-power view further demonstrates the situation and relation of arachnoid villi in coronal section. They are seen to be situated at the depth of the meshes seen in the previous figure and to protrude into and form septæ in a lacuna. H. and E. ×15.

FIG. 1.

FIG. 2.

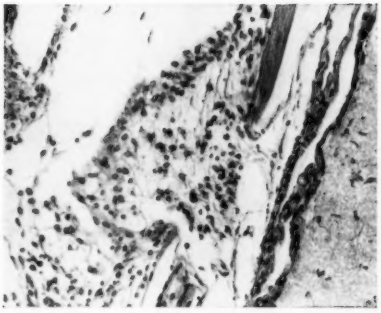

FIG. 3.

FIG. 4.

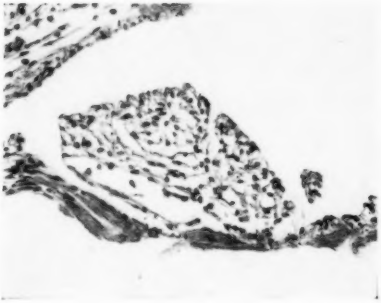

FIG. 5.

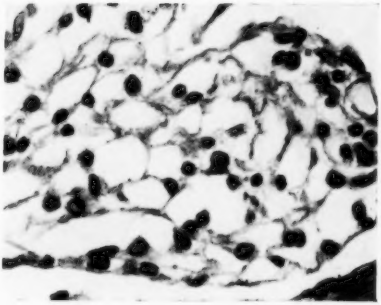

FIG. 6.

To illustrate article by Keasley Welch and Verner Friedman.

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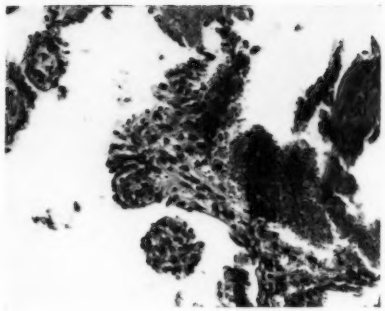

FIG. 7.

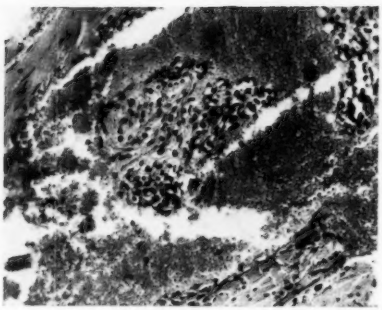

FIG. 8.

FIG. 9.

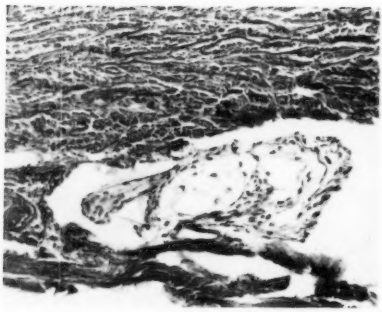

FIG. 10.

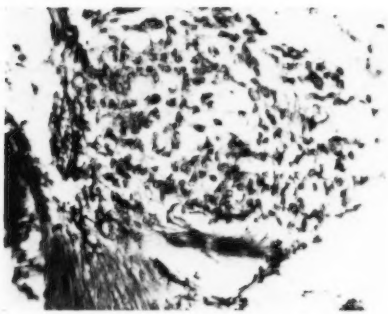

FIG. 11.

To illustrate article by Keasley Welch and Verner Friedman.

FIG. 3.—A section of an arachnoid villus which demonstrates an appearance in keeping with traditional descriptions. A tube of arachnoid leads from the surface of the brain through the dural defect. The villus is covered by a "cell cap" consisting of several layers of mesothelial cells. H. and E. ×145.

FIG. 4.—An arachnoid villus is seen to be made up of tubes of varying size, each sharing a common wall with its neighbour. From the surface, invaginations extend towards the interior and at the base a cluster of cells forms a cell cap. How the structure is surrounded, except at its base, by the contents of the lacuna is also shown. H. and E. ×145.

FIG. 5.—Another arachnoid villus is seen protruding into a lacuna. The tubular structure and the tendency for the tubes to be larger near the base are demonstrated. H. and E. ×145.

FIG. 6.—A high power view of a portion of an arachnoid villus. The tubes, varying from 4 to 12 microns in diameter, are formed by the flattened prolongations of the cytoplasm of the mesothelial cells. H. and E. ×500.

PLATE LXXV

FIG. 7.—A collapsed arachnoid villus is shown. The specimen was fixed in situ by arterial perfusion of formalin under conditions of reduced cerebrospinal fluid pressure brought about by cisternal drainage. The tubes of the villus are obliterated. H. and E. ×145.

FIG. 8.—A villus from the same animal as that depicted in fig. 7. A tubular structure can barely be discerned. H. and E. ×145.

FIG. 9.—A greatly distended arachnoid villus. The specimen was fixed by the subarachnoid instillation of formalin. The structure is so greatly blown-up that an aperture to its surface is greatly narrowed and elongated. H. and E. ×145.

FIG. 10.—An arachnoid villus fixed under the same conditions as in fig. 9. The central portion of the villus is distended at the expense of adjacent parts. HVG. ×145.

FIG. 11.—An arachnoid villus, frozen in situ in a living animal. The tissue was dehydrated and paraffin embedden without fixation. An open tubular structure is seen. Giemsa. ×145.

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THE EFFECT OF TEMPORAL LOBE AND HIPPOCAMPAL LESIONS ON AUDITORY AND VISUAL RECENT MEMORY IN MONKEYS[1]

BY

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INTRODUCTION

RECENT studies of Penfield and Milner (1958), as well as earlier reports of Scoville (1954), Scoville and Milner (1957) and Glees and Griffith (1952), have shown the importance of the hippocampal complex for normal process of retention in man. We now know that bilateral destruction of these mesial structures of the temporal lobe may cause severe and persistent disturbances of recent memory while leaving essentially intact other aspects of behaviour such as old stable memories, performance of professional skills and general intelligence.

It is regrettable that there should be so few animal experiments bearing on this topic. So far, psychophysiology has been concerned almost exclusively with the investigations of old or static memory as opposed to recent or dynamic memory. There is a large body of evidence showing that old memory traces are strikingly resistant to large cortical ablations; but in only a few recent papers by Mishkin (1954), Chow (1951, 1954), Mishkin and Pribram (1954), Pribram and Mishkin (1955), Goldberg, Diamond and Neff (1957) and Weiskrantz and Mishkin (1958), though dealing with auditory and visual discrimination and not directly concerned with recent memory *per se*, can we find the possibility that recent memory of a given sensory modality may be severely impaired following lesions of cortical areas in the immediate vicinity of the primary sensory projection areas.

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One of the reasons for this paucity of information regarding recent memory performance in animal experiments can probably be found in the lack of appropriate tests which will give a true measure of this phenomenon. As pointed out recently by Konorski (1959), the tasks that have been used in the past, such as the delayed response tests, conditioned inhibition or trace conditioned reflexes, are open to criticism with regard to their potentiality as true indicators of recent memory performances in so far as the sensory modality used in these tests is concerned. It is for this reason that he suggests the use of a testing procedure, somewhat similar to the delayed matching from sample, which eliminates most of this criticism. This test uses compound stimuli, and each stimulus is made up of two signals of the same sensory modality separated by a short interval which may be varied from one to five seconds or more. As used in Konorski's laboratory, a compound stimulus consisting of two identical signals, e.g. two tones of identical pitch, is positive and is reinforced by food if it produces the appropriate response in the animal (pressing a lever or opening a door). On the other hand, when the second signal of a compound stimulus differs from the first, e.g. two tones of different pitch, the stimulus is negative and is not reinforced, and the animal has to learn to leave the food dispensing apparatus alone. In other words, the compounds Sx-Sx and Sy-Sy etc. are positive, while Sx-Sy and Sy-Sx are negative as long as "x" differs from "y." The interesting feature in this testing procedure, and what distinguishes it from most previously used tests, is that here the first signal has no significance in itself, it can be part of either a positive or a negative compound stimulus. The correct response is possible only when the animal retains the trace of the first signal up to and including the time of the second signal so that comparison may be made between the two.

In the present series of experiments the monkeys were trained with both auditory and visual compound stimuli. When training was completed the animals underwent three types of temporal lobe excisions. The present report is concerned with the post-operative behavioural data obtained. Since the animals are being kept alive for late post-operative testing, there are no anatomical data available of these various ablations at the present time.

Material and Method

The apparatus and methods used in training these animals will be described fully elsewhere (Stepien and Cordeau, 1960) and only a brief summary will be given at this time.

I. Animals

The experiments were performed with seven completely naïve African green monkeys (*Cercopithecus athiops sabæus*). Their weights ranged from 2·5 to 5·0 kg. and the group included five male and two female animals.

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II. Apparatus

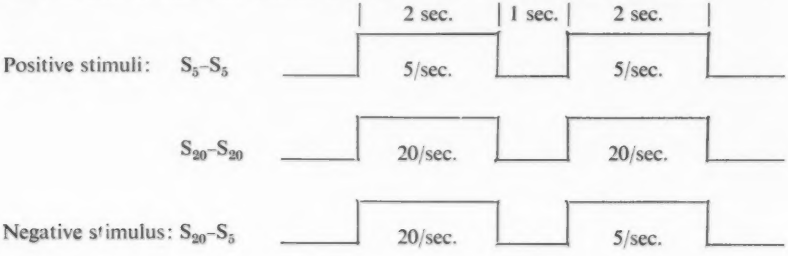
Each animal was trained and tested in its home cage. Once a day this cage was brought into the experimental room where a wooden food-box with a spring-hinged door was attached to it. The experimenter sat behind a one-way vision screen and delivered the food reward through a pipe leading into the food-box following a positive stimulus and appropriate response of the monkey, i.e. opening the door to the food-box (fig. 1, Plate LXXVI).

The animals were trained to perform with auditory and visual compound stimuli in the form of clicks and flashes of lights at variable frequencies. These were produced by an EPIPHOTE variable frequency generator connected to a noiseless neon tube stroboscope and to a loudspeaker. Both modes of stimulation could be used separately or simultaneously. An automatic timer controlled the whole sequence of the compound stimulus once initiated, and the delay between the two signals of each stimulus as well as the duration of each signal could be adjusted to any appropriate length of time. A manual two-way switch was also available for direct control of the stimulus sequence. Throughout this training no attempt was made to isolate the animal from the usual background of laboratory noises.

III. Method

(*a*) *Pre-operative training.*—In the initial stages of training the animals were first taught a simple bell-buzzer type of discrimination, the buzzer being the positive stimulus to which the animal had to open the door to receive its food, and the bell the negative or inhibitory stimulus. It was soon realized that the lack of reinforcement would not be sufficient to teach the animal to leave the door of the food-box alone at the inhibitory stimulus, or at least that training on this basis would take an inordinately long time, so punishment was introduced for wrong answers in the form of a mild electric shock to the brass knob of the door. This form of punishment was continued throughout all subsequent training.

As soon as each animal reached criterion level in this first task, it was started on auditory compound stimuli discrimination in the form of clicks at frequencies of 5/sec. and 20/sec. In the early stages this task was simplified to the presentation of two positive compound stimuli and one negative compound stimulus, each with a short interval of one second between signals of the same stimulus as follows:



After some weeks, as the animal reached criterion levels, the task was made gradually more difficult by the introduction of other frequencies within the 5 to 20 range both as positive and inhibitory stimuli and by a gradual lengthening of the intersignal interval to 5 seconds.

Simultaneously with this latter stage of training in auditory discrimination, each animal was started on the visual compound stimuli discrimination task with intermittent photic stimulation instead of clicks and using identical frequencies and

FIG. 1.—Experimental set-up used in connexion with training of monkeys in auditory and visual compound stimuli discrimination.

To illustrate article by Lucjan S. Stepien, J. Pierre Cordeau and Theodore Rasmussen.

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intervals as with the auditory signals. The transfer from one sensory modality to the other was immediate and where it had taken weeks or months to teach the animal to perform with auditory stimuli, the visual discrimination was usually complete at the end of the first test period. Here again the task was gradually made more difficult by the use of other frequencies and lengthening of the interval. One monkey, SC-3 (Tony) could not be trained with intermittent photic stimuli. From the start it was afraid of the flashing light and became extremely nervous on subsequent training with this form of stimulation which had to be abandoned.

(*b*) *Surgery*.—For the purpose of surgery the animals were divided into three groups (fig. 2).

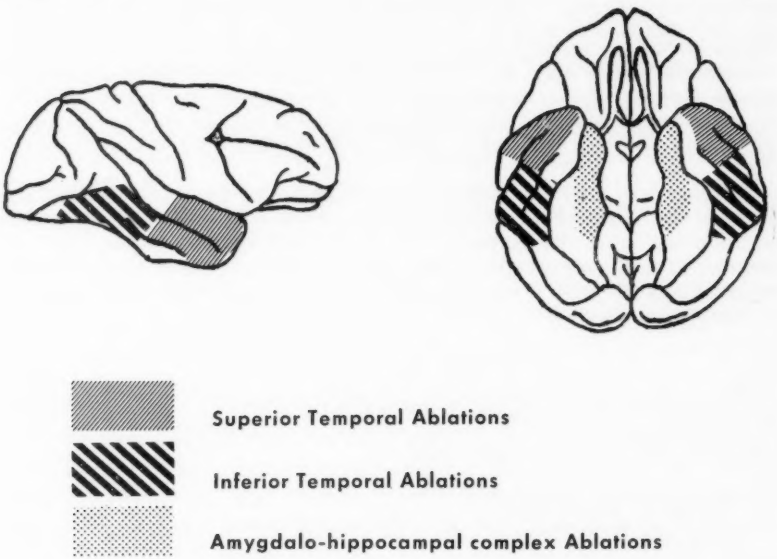

FIG. 2.—Line drawings of the brain of an African green monkey showing the cortical areas and rhinencephalic structures removed in the different surgical groups.

In the first or superior temporal group (three monkeys: SC-1, SC-2 and SC-3) the first and second temporal gyri were removed in two (SC-1 and SC-2), and the first temporal convolution only in one (SC-3). The excisions were limited to the neocortex anterior to the primary auditory areas which were left intact. This corresponded to a zone extending caudalward, approximately 20 mm. from the temporal pole, and in any case not farther than the vein of Labbe when this was present.

The second or inferior temporal group (two monkeys: SC-4 and SC-5) had the second and third temporal convolutions removed, from the vein of Labbe to a point situated 20 mm. more caudally or just in front of the inferior occipital sulcus.

Finally, the third group or amygdalo-hippocampal complex group (two monkeys: SC-6 and SC-7) had bilateral excisions of the uncus, amygdala, hippocampus and hippocampal gyrus.

Each monkey was operated in two stages, first on the right and some ten to twenty-

five days later on the left. In the interval between the two stages each animal was retested in all three tasks: bell-buzzer discrimination and auditory and visual compound stimuli discriminations. No deficit was found in any of these tasks.

(*c*) *Post-operative testing and training.*—Two weeks after the second operation each monkey was retested in all pre-operative tasks. Where a deficit was found, an attempt was made to re-train the animal using the original simplified version of the tests with two positive and one negative compound stimuli and an interval of one second between the two signals of each compound stimulus. This attempt at retraining was maintained for a minimum of 20 test periods in all cases before it was decided that the animals could not relearn their task, at least during this early post-operative period. Subsequently, re-training was continued in 3 monkeys (SC-2, SC-4 and SC-6), and a further simplification of the task introduced by the presentation of the two signals of each compound stimulus in rapid succession with no appreciable interval between the two. Under these conditions the positive stimuli became continuous signals of clicks or flashes at frequencies of 5 or 20/sec. and of four seconds' duration, while the negative stimuli, also continuous and of four seconds' duration, were made up of a first half at a frequency of 20/sec. followed immediately by a second half at 5/sec.

Simultaneously with this re-training and depending on the deficit observed, each monkey was started on a conditioned inhibition test of the same sensory modality as that of the deficit. The purpose of this new training, which will be described in the results, was to try and teach the animal a new task which did not involve the necessity of holding a first signal to compare it with a second as in the case of the compound stimuli used in pre-operative training.

Results

The post-operative data will be described under the following headings: I, General behaviour, II, Performance in pre-operatively learned tasks, and III, Performance in new learning.

I. General Behaviour

Following surgery there was no evident change in the general behaviour of the monkeys belonging to the superior and inferior temporal groups whose personality traits had become quite familiar to the experimenter. But the two animals (SC-6 and SC-7) with amygdalo-hippocampal complex excisions did show some signs of the bilateral temporal lobe ablation syndrome as described by Klüver and Bucy (1937, 1938, 1939). There was no true *psychical blindness* as described by these authors. When presented with a variety of objects (metal nuts and bolts, rubber washers, cotton-wool, blocks of plasticine, soap, etc.) amongst which were placed a few pieces of food, the animal immediately picked up the edible objects without hesitation. However, there was some form of what Klüver and Bucy described as *oral tendencies*. Following disposal of the food objects, the monkey would go on investigating the other soft objects present (cotton-wool, plasticine, soap, etc.), picking up each object in turn in more or less random sequence and bringing it to its mouth before finally rejecting it. The metal objects were left strictly alone. At its beginning

this behaviour appeared to us to be that of a normal monkey when faced with a variety of strange objects which it has never seen before. The only difference was that, here, this behaviour was continued indefinitely if the animal were left alone, each object being picked up repeatedly, sometimes only a few seconds after being discarded, and reinvestigated. From the evidence accumulating on the role of these mesial temporal lobe structures in memory functions, this behaviour would appear to be the result of a loss of recent memory rather than any oral tendency *per se*. The animal investigates these objects as a normal monkey would, but keeps on doing so as if unable to record previous experience. This lack of recent memory could also be shown by offering the animal a lighted cigarette which it would repeatedly take into its hands and burn itself.

There were also some *emotional changes* present in that the animal, when in its cage, could be approached more easily and appeared more tame than before operation. But all attempts to touch or seize it would produce the normal fear and anger reactions and it would resist violently. The only evidence of *hypersexuality* was the prompt erection in the male of this group when the experimenter approached its cage. This had not been seen pre-operatively. But when placed with another male or a female monkey, there was no attempt to mount on the part of the operated animal and no evident manifestation of sexual interest. Changes in *dietary habits* were present and both animals would eat meat when it was offered to them. There also appeared to be an overall increase in their general activity. This was more marked in the male monkey which kept jumping and climbing in its cage whenever an observer was present.

As far as the general training situation is concerned, no loss of memory was seen in any of these animals. They were all still familiar with the apparatus used and knew that to open the food box door at the appropriate signal meant a food reward.

II. Performance in Pre-operatively Learned Tasks

Following surgery all monkeys were retested in the simple bell-buzzer discrimination task and no defect found in any of them. However, marked differences between groups were present in the performance of visual and auditory recent memory tasks.

(*a*) *Superior temporal group.*—The pre-operative learning and post-operative testing of SC-1 in both auditory and visual compound stimuli discrimination is shown in fig. 3. The animal was first begun on auditory discrimination (clicks) using two positive compound stimuli S_5–S_5 and S_{20}–S_{20} and one inhibitory stimulus S_{20}–S_5 with an interval of one second between the two signals of each stimulus. It took 38 experimental sessions for this animal to reach criterion levels and from then on the task

was made more difficult by the introduction of new frequencies and a lengthening of the intersignal interval as described previously. It should be noted that once the animal had learned the simplified version of the task, the gradual increase in complexity did not alter the performance level. In other words, it was able to generalize its previously acquired knowledge that similar signals meant a positive stimulus while dissimilar signals made up an inhibitory stimulus.

Simultaneously with this increasing complexity of the auditory task, this animal was started on visual compound stimuli discrimination using

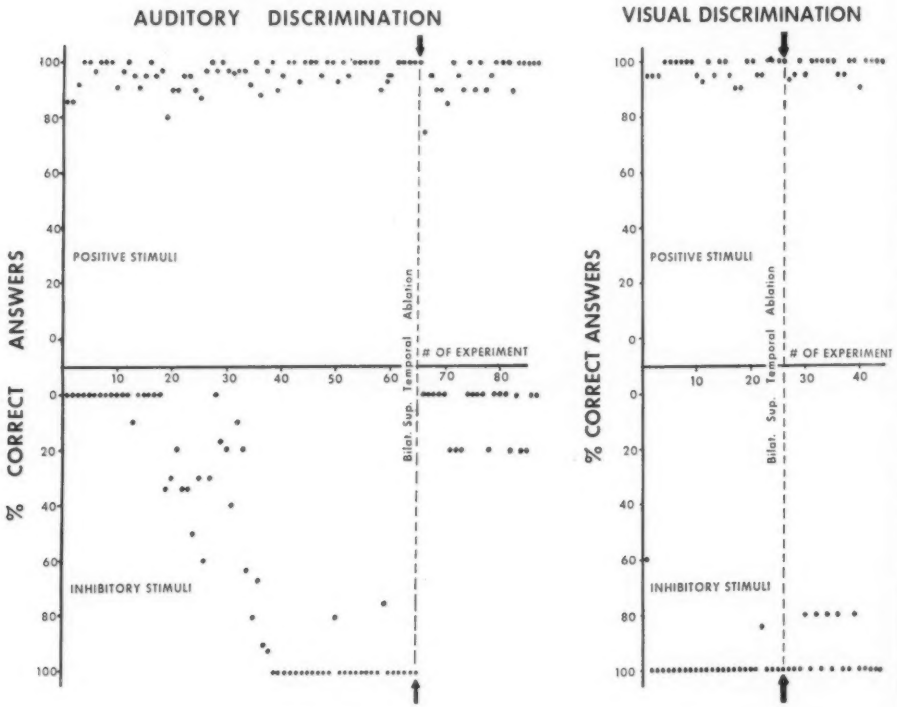

FIG. 3.—Performance data for SC-1 in pre-operative learning and post-operative testing in both auditory and visual compound stimuli discrimination. This animal belonged to the superior temporal group and surgery occurred at the broken lines. See text for further details.

flashes of light instead of clicks, the signals remaining otherwise the same in timing and frequencies. As can be seen from fig. 3, the transfer from one sensory modality to the other was nearly immediate, the animal

reaching a level of 60 per cent correct answers to the inhibitory stimuli during the first test period and 100 per cent thereafter.

Two weeks following surgery (dotted line) post-operative testing was begun. It can be seen that after bilateral excision of the first and second temporal convolutions anterior to the auditory areas, the animal could not discriminate between positive and inhibitory stimuli in the auditory field while it could still do so in the visual field. The performance level with auditory compound stimuli fell sharply while the discrimination of visual compound stimuli was only slightly affected. In other words, it appears as if the animal could not hold the first click signal for the short interval between signals so as to compare it to the second. In the post-operative testing, once the deficit had been noted with auditory stimuli, this task was simplified to its original low level of complexity with two positive and one negative stimuli and a one-second intersignal interval. The deficit remained and the animal was unable to re-learn this task during the 27 post-operative test periods even while performing adequately the visual discrimination task at its high level of complexity.

The performances of the other two monkeys in this group (SC-2 and SC-3) were similar to the one just described and are summarized in Table I. In the pre-operative columns of this table are shown the performance data from the time the animals reached criterion in auditory compound stimuli discrimination to the time of surgery. In the post-operative columns are summarized the results obtained in testing these animals after surgery. The darker figures indicate the area of the deficit.

Following the compilation of these figures, SC-3, whose bilateral excisions were limited to the superior temporal convolution, showed some slight indication that it might re-learn the auditory discrimination task. However, the results of each test period varied widely from day to day and no definite conclusion is possible at present. The outcome of this late post-operative testing in this animal will be reported subsequently, together with the long range effect of surgery in the other animals.

(*b*) *Inferior temporal group.*—Following excision of the second and third temporal convolutions from the vein of Labbe to the inferior occipital sulcus, the deficit observed was opposite to that of the preceding group. Fig. 4 shows the training curve and post-operative performance of SC-4. Here the auditory discrimination task continued to be performed at close to the pre-operative level, while the visual compound stimuli could not be differentiated. The performance of SC-5, the other monkey in this group, is similar and summarized in Table I.

(*c*) *Amygdalo-hippocampal complex group.*—As can be seen from fig. 5 and Table I, the performances of SC-6 and SC-7 after bilateral excision of the rhinencephalic structures of the temporal lobes, were

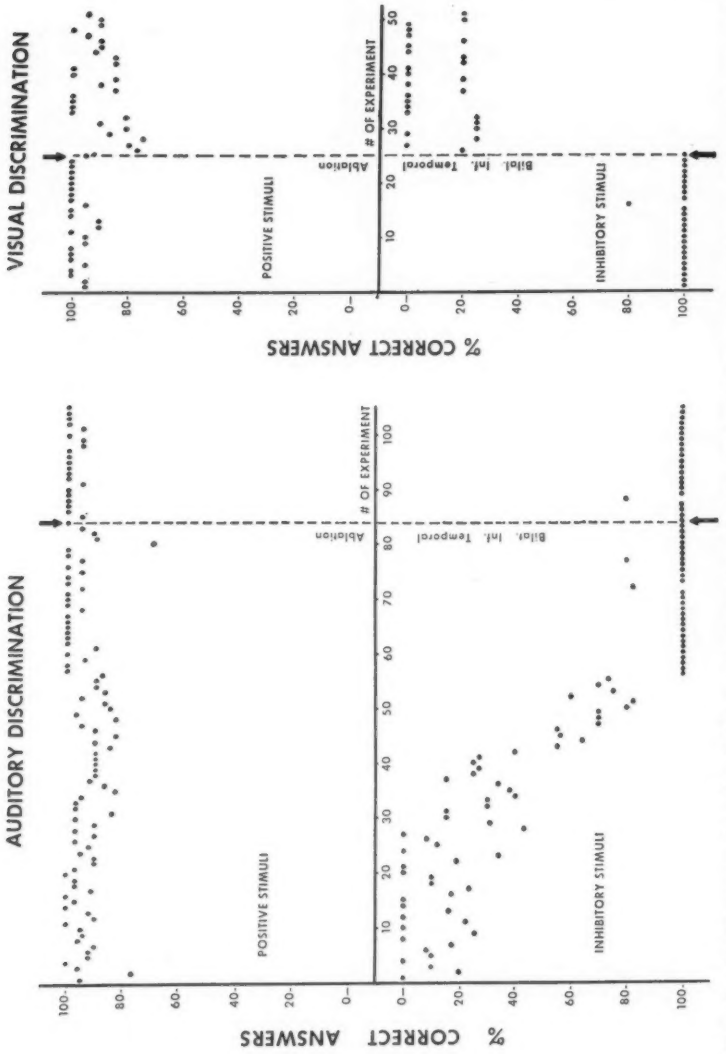

FIG. 4.—Performance data for SC-4 in pre-operative learning and post-operative testing in both auditory and visual compound stimuli discrimination. This animal belonged to the inferior temporal group.

deficient in both sensory modalities. The animals were quite incapable of performing the task either with auditory or visual inhibitory compound stimuli, even though they still remembered the general training situation but now opened the door to both positive and inhibitory stimuli.

TABLE I

Summary of pre- and post-operative performance data for each monkey in both auditory and visual compound stimuli discrimination. In the pre-operative columns are shown the data from the time the animals reached criterion in compound stimuli discrimination to the time of surgery. In the post-operative columns are summarized the results obtained in testing the animals after surgery. The darker figures indicate the area of the deficit.

SURGICAL ABLATIONS	SC 1 (Pappy)		SC 2 (Mitzy)		SC 3 (Tony)		SC 4 (Miki)		SC 5 (Baby)		SC 6 (Ami)		SC 7 (Kali)	
	Superior Temporal						Inferior Temporal				Amygdalo-Hippocampal			
I AUDITORY DISCRIMINATION	Pre Op.	Post Op.	Pre Op.	Post Op.	Pre Op.	Post Op.	Pre Op.	Post Op.	Pre Op.	Post Op.	Pre Op.	Post Op.	Pre Op.	Post Op.
a) Total No. of Experiments	28	27	20	28	13	27	28	25	12	21	13	29	11	26
b) Positive Stimuli														
Total	587	541	384	544	400	540	555	500	258	420	273	580	212	520
Correct Answers	576	513	376	470	390	514	534	492	253	401	261	551	204	475
% Correct Answers	98%	94%	98%	86%	97%	95%	96%	98%	98%	95%	96%	95%	96%	91%
c) Inhibitory Stimuli														
Total	150	135	98	135	107	135	142	125	74	105	69	145	71	130
Correct Answers	146	10	96	15	106	14	141	123	72	98	67	8	66	16
% Correct Answers	**98%**	**8%**	**98%**	**11%**	**99%**	**11%**	99%	95%	97%	94%	**97%**	**6%**	**93%**	**13%**
II VISUAL DISCRIMINATION														
a) Total No. of Experiments	25	23	19	22	-	-	24	30	11	26	11	21	11	22
b) Positive Stimuli														
Total	466	457	381	441	-	-	458	554	218	520	221	420	221	440
Correct Answers	455	445	272	427	-	-	448	503	213	488	215	404	211	401
% Correct Answers	97%	97%	98%	96%	-	-	98%	90%	97%	94%	98%	96%	95%	91%
c) Inhibitory Stimuli														
Total	119	114	96	111	-	-	118	138	59	130	55	105	66	110
Correct Answers	116	109	95	103	-	-	117	14	58	7	54	4	63	5
% Correct Answers	97%	95%	99%	93%	-	-	**99%**	**10%**	**98%**	**6%**	**98%**	**4%**	**95%**	**5%**

III. POST-OPERATIVE LEARNING

In an effort to delimit more accurately the area of the post-operative deficit in these animals, most of them were subjected to various types of new tests or modified versions of the recent memory tests which will be described in the following order: (i) Simple frequency discrimination; (ii) Conditioned inhibition; and (iii) Compound stimuli without interval between signals.

(i) *Simple frequency discrimination.*—SC-1 of the *superior temporal group* with a defect in auditory compound stimuli discrimination, was trained to perform the same task but with the use of simple click stimuli.

Here a signal of two seconds' duration with clicks at a frequency of 7/sec. was the positive stimulus and the animal had to open the door of the food-box to obtain its food reward, while a similar signal with a click

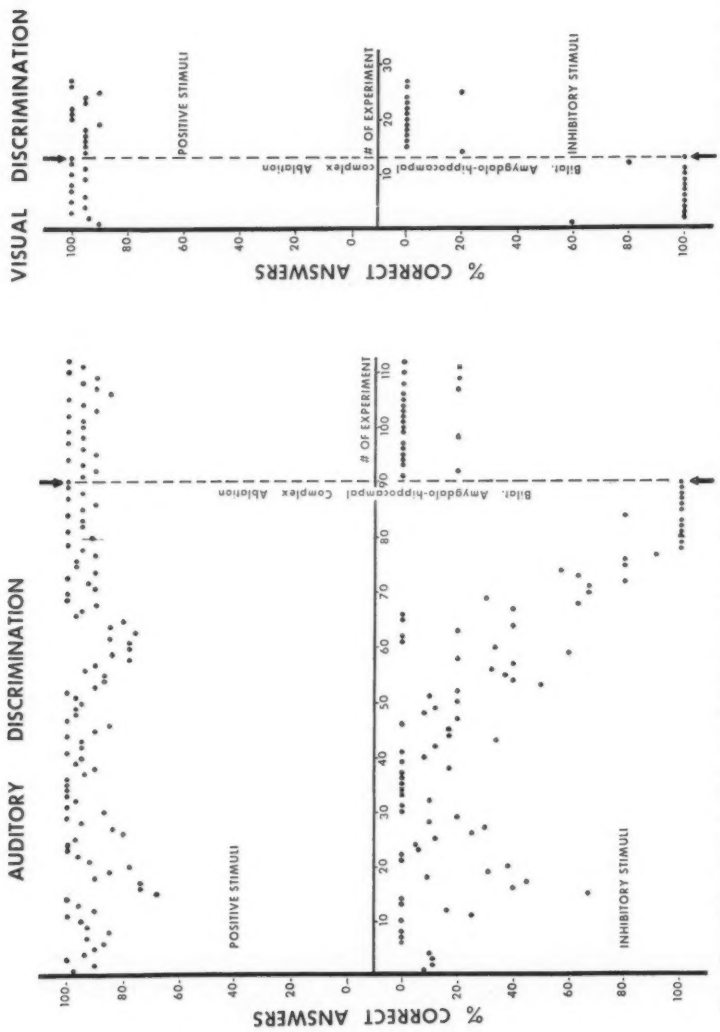

FIG. 5.—Performance data for SC-6 in pre-operative learning and post-operative testing in both auditory and visual compound stimuli discrimination. Bilateral excision of the rhinencephalic structures of the temporal lobes occurred at the broken lines.

frequency of 17/sec. was the inhibitory stimulus and the animal had to refrain from touching the door. SC-4 of the *inferior temporal group* with

a deficiency in the visual field was similarly trained with simple intermittent photic signals at frequencies of 7 and 17/sec. These being quite sophisticated animals at this stage the task was learned very rapidly and in both cases differentiation was complete at the end of the first training session, the performances remaining at the 100 per cent level both for positive and inhibitory stimuli thereafter. Therefore it appears that the deficit in these animals did not reside in their capacity to differentiate click or flash signals at different frequencies.

(ii) *Conditioned inhibition.*—Here again the monkeys had to perform the same task using cues of the same sensory modality as that of their deficit in compound stimuli testing. SC-1, SC-2, SC-3 and SC-6, all with auditory deficits, were trained with the buzzer as the conditioned stimulus and a whistle as the conditioned inhibitor. The buzzer signal was already strongly established as a positive stimulus in these monkeys from their bell-buzzer discrimination test, but now the animal had to learn that when preceded by a whistle blast the buzzer signal which followed after a short interval became negative, and opening the door of the food-box after the complex whistle-buzzer meant punishment rather than reward. In the initial stages of training the interval between the whistle blast and the buzzer signal was made short, i.e. approximately 1 second, and was gradually lengthened to 8 and 10 sec. in subsequent test periods.

SC-4 and SC-5, with a defect in the visual compound discrimination, were trained in a similar conditioned inhibition test using a white lamp, illuminated for two seconds, as the positive or conditioned stimulus and a red lamp as the conditioned inhibitor. In other words, on presentation of a white light for two seconds the animal was to open the door and receive its food reward. However, if this white light were preceded by a red light the animal was to refrain from touching the food dispensing apparatus. Here again the interval between red and white light was gradually lengthened to 10 seconds.

All animals learned this task readily and training was usually completed in four to five training sessions. Therefore it appears that these monkeys could learn a new task involving delays greater than those of the recent memory tests. One of the major differences between the two, of course, is that in the compound stimuli discrimination for recent memory the animal has to "hold" the first signal and compare it with the second, while in the conditioned inhibition test, the conditioned inhibitor (whistle or red light) is in itself significant and determines the positive or inhibitory quality of subsequent signals. The animals reacted quite differently to the two modes of stimulation. With presentation of the first signal of the compound stimulus in the recent memory task, the monkey would wait expectantly for the second signal by the door of the food box, but hurried to the far corner of its cage on presentation of the conditioned inhibitor,

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where it remained during the whole interval and presentation of the conditioned stimulus.

(iii) *Compound stimuli discrimination without interval between signals.*— Finally, and as described previously, the attempt at retraining in compound stimuli discrimination was continued in three monkeys with a further simplification of the testing procedure. In this instance the interval between the two signals of each compound stimulus was made as close to zero as possible. This change meant that the positive stimuli at frequencies of 5/sec. or 20/sec. became continuous and of four seconds' duration, while the negative stimulus, also of four seconds' duration, consisted of a first half at 20/sec. and a second half at 5/sec. without appreciable interval between the two. One monkey from each of the three surgical groups was tested in this way, using stimuli of the same sensory modality as that of their deficit, SC-2 and SC-6 with auditory clicks and SC-4 with flashes of light.

The performances of all three animals improved immediately and, even though the per cent correct answers for the inhibitory stimuli rarely reached the pre-operative levels, it was quite evident that the animals could perform the task in the absence of an appreciable interval between signals. After six test periods with high levels of performance, the delay between signals was increased to its original value of one second and once more the three monkeys became incapable of differentiating between positive and negative stimuli. This would make it appear that the short delay between signals is the main component in the difficulty of the task, and would seem to point once again to a deficit in recent memory or "holding" capacity in these animals.

Discussion

In this section we propose to discuss in turn the nature of the deficit found in each of our three groups of animals. However, before we go into this we feel that the phenomenon of transfer of compound stimuli discrimination from one sensory modality to another deserves brief mention. It was reported in the results that after weeks or months of training in auditory compound stimuli discrimination, and on reaching criterion levels in the performance of this task, the animals were started each in turn, on the visual discrimination task with signals at similar frequencies. We were hoping that this new training would be shorter than, and facilitated by, the previous experience of these animals in auditory compound stimuli discrimination but we were not prepared for the extreme rapidity with which this transfer occurred. In all animals but one it took less than one training session, made up of 20 positive and 5 negative stimuli, for the differentiation to be complete in the visual field. This should be compared to the more than a thousand positive and

several hundred negative stimuli necessary to obtain differentiation in the initial auditory training. It has been suggested to us that the monkey is a "visual" rather than an "auditory" animal, that it relies on visual rather than on auditory cues to solve problems in its natural habitat, and that the reverse sequence of training and a measure of transfer from the visual to the auditory field would be necessary for a proper appreciation of the magnitude of this phenomenon. This may well be the case, but we believe that the discrepancy between the times necessary to train these animals in auditory and visual signals in the present sequence is too great to be accounted for by anything but an active physiological process which facilitates the transfer of memory traces of rhythms from one sensory modality to another.

We should not have been quite as surprised at the rapidity of this transfer had we known more of the literature on this subject. In 1926 it was shown by Rosenthal that differentiation of two frequencies of rhythmic tactile stimulation of the skin in one area is easily transferred by the animal to other skin areas. Experimentation of this type was developed by Dolin (1937), who showed that the differentiation of two rhythmic stimuli of a given sensory modality (e.g. beating of a metronome) is not only transferred to rhythmic stimuli of the same modality (bells, etc.), but also to other sensory modalities such as the rhythmic lighting of a lamp. In other words the rhythm is, so to speak, abstracted by the animal from the other characteristics of the stimuli. Similar phenomena are of common occurrence in the higher nervous activity of man. Thus a certain tune, i.e. a combination of sounds, is recognised regardless of the key in which it is played (for a discussion of this subject *see* Konorski, 1948). The underlying physiological mechanism is unknown and it has been speculated (Konorski, 1948) that this transfer phenomenon involves structures at a "higher level" of nervous system activity than the specific sensory projection areas. In view of recent electrophysiological findings in conditioning (Yoshii, Pruvot and Gastaut, 1956; Yoshii, Matsumoto and Hori, 1957), and in line with Penfield's concept of the centrencephalic system (Penfield, 1954; Penfield and Jasper, 1947), the possibility that subcortical centres play a major role in this phenomenon of transfer should be kept in mind and made the subject of further study.

I. Auditory Deficit in Superior Temporal Monkeys

Within the limits of our testing procedure, the animals with superior temporal ablations were incapable of differentiating between positive and inhibitory compound stimuli in the auditory field but could still do so quite adequately with visual stimuli. Several possible explanations would account for such a deficit.

The first and most obvious is that these animals could have become

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deaf following surgery. However, the primary auditory areas in these monkeys were spared and there is no evidence of a loss of auditory acuity even though no formal testing was done.

The deficit could also be accounted for by a loss of rhythm differentiation in the auditory field. It is quite evident that if the superior temporal monkeys could not tell the difference between click signals at different frequencies, it became quite impossible for them to discriminate between stimuli made up of similar signals and others of dissimilar signals. This possibility appeared unlikely in view of the demonstration by Butler, Diamond and Neff (1957) and Neff (1957, 1958) that the complete and bilateral excision in cats of all auditory areas AI, AII and Ep leaves frequency differentiation intact. However to test this hypothesis the animals were trained to differentiate between two click signals, one at 7/sec. and the other at 17/sec, and as noted in the results, this task was learned easily.

It could also be argued that the surgical removals produced a non-specific type of deficit which lowered the animals' general ability to react to any kind of complicated training situation or, as Lashley expresses it, "a general impairment such as a loss of comparison attitude or a lowering of vigilance." This seems to be disproved in this group, at least by the fact that these animals could still perform the same discrimination in visual compound stimuli while incapable of doing so in the auditory field.

On the other hand, the impairment may be limited to the sensory modality involved. In other words, superior temporal monkeys may be incapable of performing any complex discrimination using auditory signals as cues. This possibility remains. It is, however, made unlikely by the demonstration that these animals learned readily to perform the task with the compound stimuli of the conditioned inhibition test (*see* results). It seems that these animals can learn tasks of the same sensory modality as their post-operative deficit and can perform these tasks with delays greater than those of the test in which they are deficient, the main difference of course being that in the conditioned inhibition test the first signal is significant by itself and does not have to be held for comparison with a second signal. Furthermore, the fact that one animal of this group could discriminate between positive and negative stimuli when the inter-signal interval was reduced to zero and could not do so when this interval was once more lengthened to one second, would appear to be another argument in favour of a deficit in recent memory mechanisms within the limits of our testing procedure.

The literature dealing with this subject is rather limited. Similar experiments were performed with dogs by Chorazyna and Stepien (1959) in Konorski's laboratory, using tones of similar or different pitch as

components of the compound auditory stimuli. They reported that in animals so trained the bilateral excision of the Sylvian gyrus, leaving the auditory cortex intact, permanently impaired the performance of this task. As in our monkeys, their dogs appear to be unable to hold the first signal so as to compare it with a second, and this deficit is still present more than one year after surgery. Similar lesions in the cat, i.e. ablation of the insular and temporal cortex ventral to the second auditory area AII, leaving the latter intact, have been shown to result in a severe and probably complete loss of tonal pattern discrimination (Goldberg, Diamond and Neff, 1957; and Neff, 1957, 1958). The test used involved discrimination of two patterns, one consisting of three tonal pulses in the sequence "low-high-low," and the other of the same tones presented in the sequence "high-low-high." The ablation in cats of this "ventral auditory area" was shown to produce degeneration in the posterior pole of the medial geniculate body, pars principalis (Rose and Woolsey, 1958; Diamond, Chow and Neff, 1958). The corresponding area in the monkey lies on the superior temporal plane immediately rostral to the classical auditory area (Akert, Woolsey, Diamond and Neff, 1959). It was in fact these anatomical studies which directed our surgery to the first temporal convolution and we would expect our superior temporal monkeys to show a similar deficit as that found in cats with insular and temporal cortex ablations. It could be assumed that in the latter group, discrimination of the two tonal patterns "low-high-low" and "high-low-high" involves some form of recent memory since the animal must probably "hold" the first signals of each pattern for comparison. But since only two frequencies were used for both positive and negative stimuli, it could be argued with Konorski (1959) that the first tone (or the last) in each pattern determines the positive or negative quality of the whole stimulus depending on whether it is "high" or "low." It would have been interesting to see if prior to surgery these cats could have generalized their knowledge to tones of other frequencies arranged in similar patterns of "low-high-low" and "high-low-high." This would have been an argument that recent memory is probably involved in this type of discrimination rather than recognition of the first or last tone in the sequence.

II. Visual Deficit in Inferior Temporal Monkeys

The deficit in this group of monkeys was opposite to that found in the superior temporal animals, i.e. they were incapable of differentiating between positive and inhibitory compound stimuli in the visual field while they could still do so with auditory stimuli.

As in the preceding section, the same line of argument based on experimental facts could be used to show that (1) these animals were not blind and did not appear to suffer from a loss of visual acuity (*see also* Ettlinger,

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1959); (2) their deficiency did not lie in an incapacity to differentiate between two flash frequencies since they could still differentiate between two single intermittent photic signals at frequencies of 7/sec. and 17/sec.; (3) there was no general impairment to perform tasks using visual cues since they learned the conditioned inhibition test using red and white lights with delays greater than those of the test in which they were deficient; and finally (4) the deficit appears to be one in the "holding" mechanism since discrimination between positive and negative visual compound stimuli became possible when the intersignal interval was reduced to zero but failed when this interval was lengthened to its original value of one second.

The literature dealing with visual discrimination and localized ablations of the visual or temporal cortices is much more extensive than that dealing with auditory discrimination and corresponding excisions, and it is not our intention to discuss it at length here (for recent reviews *see* Milner, 1954; Jasper, Gloor and Milner, 1956). But in so far as the deficits in visual discrimination produced by cortical ablations outside the visual areas proper are concerned, the work of Ades and Raab (1949), Chow (1951, 1952, 1954), Mishkin (1951, 1954), Poirier (1952), Mishkin and Hall (1955), Pribram and Mishkin (1955), Weiskrantz and Mishkin (1958), has established the importance of the ventromedial temporal cortex in this respect as opposed to other areas of the temporal or parietal neocortex. To the deficits in form or colour pattern discriminations, already reported following bilateral lesions in this area, may be added from the present results an apparent difficulty in visual retention whereby the animal cannot hold a first rhythmic light signal so as to compare it with a second.

In a recent paper Pribram and Mishkin (1956) have shown that inferotemporal monkeys can achieve a higher standard of performance than antero-frontal animals in an object alternation test. The correct choice in this test is thought to depend on recent memory of the preceding cue. However both groups of operatees were made up of highly sophisticated monkeys with a long training experience and comparison with intact naive animals is not possible. The reason for the apparent discrepancy between their results and ours is not known. It could be argued that retention of a rhythmic light signal is a more difficult task or involves different mechanisms than retention of a visual image, but this is probably too naive an explanation.

Of course it cannot be claimed that the ablations reported here are the only ones which will impair recent memory performances in monkeys. It is probable that extensive bilateral destructions of the primary auditory or visual cortices, or lesions of the subcortical regions with which they are connected, would produce comparable if not greater deficits in this respect but this is a matter for further experimentation. However, the

interesting fact which emerges from these findings and other reports of recent years already quoted, is the demonstration that cortical areas outside the primary projection areas are essential for normal perceptual function in monkeys and other species.[1] The mechanism whereby this extrasensory cortex contributes to normal perceptual function is still a matter for speculation. Some hypotheses have been put forward recently (Neff, 1957), but there is little in the line of electrophysiological evidence to support them. The most that can be said is that in view of the transcortical and subcortical connections of these extrasensory cortical areas, it can probably be assumed that their destruction causes a disruption of the circuitry essential for the proper establishment of recent memory traces.

III. Deficit in the Amygdalo-hippocampal Complex Monkeys

In our 2 monkeys with bilateral ablations of the uncus, amygdala, hippocampus and hippocampal gyrus, the deficiency was not modality specific but was present for the two modalities tested, i.e. auditory and visual. Here again it was shown that in one of these monkeys it was possible to establish a conditioned inhibition of type response using a whistle as the conditioned inhibitor and the buzzer as the conditioned stimulus and with delays as long as eight seconds between the two. This seems to argue against the possibility of a general impairment in learning capabilities. To our mind this new learning would also eliminate the hypothesis that the bad post-operative performance of these monkeys is due to a lowering of the motivational factor involved (Jasper, Gloor and Milner, 1956), the animal becoming indifferent either to punishment or reward.

Another possible explanation for the post-operative deficit might be considered here. This is that the bilateral amygdalo-hippocampal complex ablations result in a deficiency similar to that found in animals with frontal lesions where classical delayed response type of tests are seriously impaired (Jacobsen, 1935). That this is not the case is shown by the results of Orbach, Milner and Rasmussen (1958), who report that in animals with lesions involving the amygdalo-hippocampal complex bilaterally the classical delayed response test is not impaired. Furthermore the fact that one monkey in this group has learned to perform with a conditioned inhibition test involving delays of eight seconds would appear to be a strong argument against this hypothesis.

So in this group also the deficit as shown by our testing procedure appears to reside in the impossibility for the animal to hold a first signal long enough to compare it with a second. This deficiency in the recording of recent memory traces is in close agreement with the recent reports of

[1]For similar findings in the importance of the posterior parietal cortex in somesthetic learning *see* Blum, Chow and Pribram (1950) and Blum (1951).

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Glees and Griffith (1952), Scoville and Milner (1957) and Penfield and Milner (1958), showing a somewhat similar impairment in man after bilateral lesions of these mesial temporal lobe structures. The mechanism whereby these rhinencephalic portions interact with neocortical functions in perceptual discrimination and memory recording is unknown. To quote at length from a recent paper by Jasper and Rasmussen (1958): "We may assume that separate projections of neocortical and rhinencephalic structures to common centrencephalic systems of the brain-stem are of critical importance as proposed by Dr. Penfield. Such a conception has definite anatomical and neurophysiological support. On the other hand, rhinencephalic formations may act as an intermediate way station in the conduction of impulse patterns for neocortex to brain stem or conversely for impulses arriving to the cortex from subcortical structures. Further speculation is not justified until we have more knowledge of the actual neurophysiological mechanisms involved in the establishment of synaptic circuits which serve to record experience in a more or less permanent manner and the mechanisms whereby these circuits are reactivated in the recall of conscious experience."

Summary

Seven African green monkeys were trained in auditory and visual recent memory tests according to a method proposed by Konorski (1959). This method requires that the animal discriminates between two series of compound stimuli, each stimulus consisting of two signals of the same sensory modality and separated by a short interval. If the two signals of a given stimulus are identical, then the compound is positive and the animal opens a door to obtain its food reward; if the two signals are different the stimulus is negative and not reinforced. In other words, the correct response is possible only when the animal retains the trace of the first signal up to and including the time of the second signal so that comparison can be made between the two.

Following training, all animals underwent surgery. In three monkeys the first and second temporal convolutions, anterior to the primary auditory area, were removed bilaterally. In two more the bilateral lesions were limited to the postero-inferior temporal cortex; the rhinencephalic portions of the temporal lobes were removed in the last two. Post-operative testing has shown the first group to be deficient in auditory compound stimuli discrimination while still capable of performing the pre-operatively learned task with visual stimuli. The reverse was true for the inferior temporal monkeys, and the amygdalo-hippocampal monkeys were deficient in both sensory modalities.

The nature of the test used, together with the results obtained in post-operative learning of new tasks during control experiments, strongly suggest that the deficit in these animals is one of recent memory in the sensory modality involved.

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EXPERIMENTAL STUDIES ON THE INNERVATION OF THE MUCOUS MEMBRANE OF THE GUT

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THE nerve supply of the gut has been the subject of intensive histological investigation ever since Remak (1840, 1852) observed the presence of microscopic ganglion cells with processes in the wall of the pharynx and of the stomach. Meissner (1857), Billroth (1858) and Auerbach (1862, 1864) made detailed examinations of the submucous, mucous and muscle layers respectively in the gut and discovered nerve plexuses which were similar in many respects to neural elements elsewhere in the autonomic nervous system. Each of the plexuses in the submucous and muscle layers of the gut wall was shown to contain aggregations of nerve cells in ganglia linked by bundles of fine nerve fibres, some of which were continuous with similar bundles of fibres in the mesentery of the gut.

With the advent of specific methods for demonstrating neural structures, the connexions between the various plexuses of the gut wall were defined more clearly. Drasch (1881), using gold chloride after formic acid fixation, drew attention to the tiered arrangement of the submucous plexus, illustrating it as consisting of outer, middle and inner divisions which are linked together and connected externally with the myenteric plexus and internally with the mucosal plexus.

Dogiel (1895, 1896, 1899) classified the neurons of the gut wall, in specimens stained with methylene blue, according to the length of their processes. He believed that the neurons which give rise to short processes (designated type I cells) were motor to the musculature of the gut, whereas the neurons with long processes (type II cells) were sensory in nature.

Dogiel's concept that motor and sensory functions are mediated by morphologically distinct neurons has received little support. According to most investigators the enteric neurons are either motor or associative

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in function and differences in the form of the cells are assumed by some to be related to a difference in their preganglionic nerve supply (Lawrentjew, 1929, 1931; Müller, 1921; Langley, 1922; Johnson, 1925; Hill, 1927; Sokolowa, 1931; Iljina and Lawrentjew, 1932; Kolossow and Sabussow, 1932; Botár, Battancs and Becker, 1942; Habel, 1956; Gunn, 1959). On the other hand, the anatomical evidence which has been presented in support of Dogiel's view that some enteric neurons are sensory in function is inconclusive. Kuntz (1922) traced nerve fibres from the submucous plexus into the mucous membrane and suggested that some of the fibres were likely to have arisen from afferent neurons in submucous ganglia. Waddell (1929) found that nerve fibres persisted in the mucous membrane of the small intestine of dogs after division of a single mesenteric neurovascular trunk and assumed that they represented mucosal processes of enteric neurons in the submucous plexus. However, Waddell apparently did not consider the possibility that an overlap in the peripheral distribution of mesenteric nerve fibres terminating in the gut wall might account for the presence of intact fibres in the mucous membrane of the operated segment of gut. Furthermore, the survival period which was selected was from fifteen to sixty days and it is possible that, during this time, an invasion of the "denervated" portion of gut by nerve fibres from adjacent normal areas had occurred, similar to that which Zander and Weddell (1951) found in the cornea. Cajal (1911), Iwanow and Radostina (1933) and Cavazzana and Borsetto (1948) demonstrated that some of the nerve fibres which link the myenteric and submucous plexuses are processes from neurons in submucous ganglia. Thus, connexions exist by means of which neurons in submucous ganglia, if, indeed, they are afferent in nature, can influence structures in the outer layers of the gut wall. Iwanowa (1958) and Kadanoff and Spassowa (1959) ascribed a sensory function to bipolar and unipolar neurons in the gut. However, enteric neurons with this appearance were described previously by Hill who found that their terminations were indistinguishable from the terminations of multipolar neurons.

Richardson (1958), in a study of the myenteric plexus of the gut of the rabbit made with the aid of the electron microscope, has demonstrated clearly the profusion of fine nerve fibres, even in a limited segment of gut and the impracticability of tracing enteric fibres to their terminations with the aid of the light microscope. Indeed, the difficulty in following the course of individual nerve fibres has led many authors to postulate a syncytial arrangement of neurofibrillar connexions between neural and non-neural elements in the gut (Stöhr, 1932, 1952, 1954; Leeuwe, 1937; Hillarp, 1946; Jabonero, 1948, 1954, 1958; Greving, 1952; Meyling, 1953; Kuntz and Napolitano, 1956). It appears unlikely, therefore, that the functional significance of the enteric neurons can be determined from evidence from morphological studies alone.

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Recent anatomical and physiological observations have led to a renewal of interest in the possible function of various components of enteric plexuses. Kuntz (1940), Kuntz and Saccomanno (1944) and Graham Ross (1958) have shown that when mesenteric nerve fasciculi are severed experimentally, many nerve fibres in the fasciculi peripheral to the level of section do not undergo degenerative changes. Thus, the possibility exists that the fibres which remain normal in appearance are processes from neurons in the enteric plexus which project centripetally within the mesenteric fasciculi. Physiological studies on reflex activity involving mesenteric fasciculi also suggest the presence in the colon of enteric neurons which project at least as far as the inferior mesenteric ganglion (Job and Lundberg, 1952; McLennan and Pascoe, 1954).

There are many descriptions by neurohistologists of "afferent" nerve fibres ending within the various layers of the gut wall, including the mucous membrane (Retzius, 1892; Berkley, 1893; De Witt, 1900; Carpenter, 1918, 1924; Hill, 1927; Harting, 1934; Nonidez, 1946; Ohi, 1954*a* and *b*; Ottaviani, 1940; Sotelo, 1954; Sugamata, 1955; Toyota, 1955; Kutsuzawa, 1956; Seto, 1956; Yamamoto, 1957; Jabonero, 1958), but none of these investigators has determined experimentally the origin of the fibres which are said to be afferent. However, workers in Japan have demonstrated degenerated nerve fibres in the intestines from four days after division of the dorsal roots of spinal nerves peripheral to spinal ganglia (Makino, 1955; Wang, 1955; Lee, 1956*a* and *b*).

It is probable therefore that some of the extrinsic afferent fibres in the gut are peripheral processes from the visceral afferent neurons in spinal ganglia which have been described by a number of authors (Edgeworth, 1892; Langley and Anderson, 1894; Langley, 1903; Chase and Ranson, 1914; Ranson and Billingsley, 1918; Rossi, 1922). The presence of afferent fibres in the vagus nerves, the location of their cells of origin and their peripheral distribution have been recorded by many authors (Chase and Ranson, 1914; Harper, McSwiney and Suffolk, 1935; Agostoni, Chinnock, Daly and Murray, 1957). Afferent fibres proper to the vagus have their cell-station in the nodose ganglion (Ranson, 1921; Mohiuddin, 1953; Evans and Murray, 1954), although the nerve trunks in the thorax may contain additional afferent fibres which have joined them from the sympathetic chain.

There is ample neurophysiological evidence that the gut is innervated by afferent fibres (Balchum and Weaver, 1943; Downman and McSwiney, 1946; Gernandt and Zotterman, 1946; Downman, McSwiney and Vass, 1948; Downman, 1952; Paintal, 1954, 1957; Iggo, 1955, 1957). Ranson's (1921) statement that small unmedullated fibres, as well as medullated fibres, are concerned in conveying afferent impulses from the gut has also been confirmed by electrophysiological studies.

From an examination of studies on peripheral autonomic fibres in the

gut as well as in other situations, it appears to have been generally assumed that degenerative changes in these fibres resulting from experimental division or pathological involvements are similar in form and time-sequence to those occurring in somatic nerves. In many accounts, degenerative changes in fibres which have been severed from their parent cells are recorded as commencing after an interval of three days and persisting for as long as twenty-one days. Few of the investigators concerned appear to be familiar with the accounts by Langley and Anderson (1894) and Tuckett (1896) which deal with the structure and degeneration of autonomic nerve fibres in the cat and the rabbit. According to Tuckett, there is both histological and physiological evidence that degeneration in unmedullated nerve fibres begins within twenty-four hours after they have been severed and is completed within forty hours. It is clear, therefore, that a reinvestigation of the form and time-sequence of degenerative changes in severed enteric nerve fibres is necessary before attempting to demonstrate the distribution of nerve fibres reaching the gut by the alteration in form that they undergo when severed experimentally.

On structural grounds, it is apparent that the neural structures in the gut are linked intimately with other parts of the autonomic nervous system, although the detailed relationships between the extrinsic and intrinsic components of the enteric plexuses are still incompletely understood (Schwab, 1931; Stöhr, 1952; Kuntz, 1953). There is ample physiological evidence, however, that the neural structures in the gut have a degree of autonomy not apparent in the remainder of the autonomic nervous system. Bayliss and Starling (1899) demonstrated that excised portions of the intestine, when stimulated, respond by contraction proximal to, and relaxation distal to the point of stimulation. This phenomenon, which was described as the "law of the intestine," they believed was due to a local nervous reflex. Subsequent investigations by a large number of workers showed that while intestinal musculature has an inherent capacity to contract rhythmically and independently of any nervous control whatever (Alvarez and Mahoney, 1922, and others), contraction of intestinal musculature in one part of the gut associated with relaxation in a part immediately adjacent, as in the propulsion of intestinal contents, is dependent on an intact nerve supply. Thus, when an isolated segment of gut, suspended in Tyrode solution, is distended by an increase in the intraluminal pressure, there results in the intestinal musculature a wave of contraction which passes from the proximal to the distal end of the segment of gut. This integrated response to distension, known as the peristaltic reflex, is abolished by local anæsthetics, by nicotine, or by atropine, while myogenic contraction which is independent of a nerve supply persists (Raiford and Mulinos, 1934; Alvarez, 1948).

Bülbring, Lin and Schofield (1958) have presented evidence which suggests that in the small intestine the peristaltic reflex is dependent on the

integrity of mucosal processes of enteric neurons, and that nerve impulses transduced at the mucous membrane reach the intestinal musculature through intrinsic nerve pathways which include at least one synaptic interruption. In the light of these observations the nerve plexuses of the gut have been re-examined in an attempt to determine the structure and connexions of neural elements which are present in the mucous membrane.

Material and Methods

Normal Animals

Portions of the alimentary tract distal to the pharynx were examined in 15 rodents (8 rats, 3 mice and 4 guinea-pigs) and 5 rabbits selected at random and without reference to litters, sex, feeding habits or age, beyond excluding animals younger than one month. Specimens taken at intervals along the length of the gut from 4 cats, 2 baboons and 3 rhesus monkeys were also examined.

Experimental Animals

Operations were performed on adult rats and cats anæsthetized with ether and intraperitoneal sodium pentobarbitone respectively.

A. *Division of Neurovascular Bundles in the Mesentery of the Small Intestine*

The following procedure, which was performed in 16 rats and 10 cats, is similar to that described by Graham Ross (1958). A portion of the jejunum or ileum was selected at which the terminal arterial arcades consisted of relatively large vessels. Mesenteric neurovascular bundles opposite the arcades were each ligated twice and the mesentery cut between the ligatures so that the loop of small intestine received blood from the vessels at either end of the divided mesentery. In the present study, the term "operated segment" refers to that portion of the small intestine between points where the arteries in the adjacent unoperated mesenteric bundles entered the peripheral arterial arcades. It was found during the course of the study that no more than three consecutive neurovascular bundles could be ligated in rats without producing apparent stasis of blood in the operated segment. The length of the operated segment of small intestine was from 3 to 7 cm. in rats and from 5 to 20 cm. in cats. No change in the colour of the denervated segment of gut was seen at the completion of the operation and at the end of the appropriate survival period. The animals were killed at intervals of from four hours to fourteen days after operation. A number of rats, in which the viability of the operated segment was impaired by dividing four or five mesenteric neurovascular bundles, were also included in this study.

B. *Division of Spinal Nerves Peripheral to Spinal Ganglia*

The spinal cord and, in some animals also the cauda equina, were exposed by dorsal laminectomy caudal to the level of the fifth thoracic vertebra. The spinal nerves were divided on each side, immediately lateral to the ganglia, from T6 to L4 (10 rats), from T5 to T11 (4 cats) and caudal to L6 (10 rats, 1 cat). The animals were killed at intervals of from four hours to four days after operation. In the animals which survived longer than twelve hours, the urinary bladder was emptied by digital pressure on the lower abdominal wall.

Method of Fixation

Specimens of gut were fixed for at least ten days in 10 per cent formalin (analytical reagent) containing marble chips.

In smaller animals, the upper part of the œsophagus and the lower end of the

rectum were ligated and fixative was introduced into the lumen with a syringe so that the whole gut was distended to an extent sufficient to smooth out any abrupt irregularities in its contour. In larger animals, segments of the gut were isolated between two ligatures and similarly distended with fixative.

Staining Method

(1) Frozen sections (50—200 μ thick) and teased preparations of gut were taken through 50 per cent and 70 per cent solutions of alcohol and were post-fixed in 95 per cent alcohol for at least one hour.

(2) After clearing in 100 per cent pyridine, the specimens were rinsed in several changes of distilled water.

The above two steps in procedure were found to be beneficial in staining neural tissue in the gut, but are not essential in staining neural tissue elsewhere.

From this point onwards a glass rod was used in transporting the preparations.

(3) After impregnation in 20 per cent silver nitrate for 10 minutes, the specimens were blotted on filter paper and placed successively in solutions of 10 per cent formalin (A.R.) and 2 per cent formalin (A.R.), each containing 1·0 ml. of 100 per cent pyridine per 100 ml., over a period of 2 to 3 minutes.

(4) The preparations were then blotted on filter paper and immersed for 8 to 20 seconds in 20 per cent silver nitrate to which ammonium hydroxide (S.G. 0·88) had been added in amounts in excess of that necessary to redissolve the precipitate.

(5) The specimens were blotted and placed in a 10 per cent formalin (A.R.) solution, containing 1·0 ml. of 100 per cent pyridine per 100 ml., until the preparations were golden brown in colour.

(6) After fixation in 5 per cent sodium thiosulphate the preparations were rinsed, dehydrated, cleared and mounted in Canada balsam.

Portions of neurovascular bundles from the mesentery of the small intestine were stained in block, with more prolonged immersion in both silver solutions, embedded in paraffin and sectioned longitudinally at 8 μ.

Observations

Neural Structures in the Gut of Normal Animals

Neural tissue, arranged in plexuses, was found in the subserous, myenteric, submucous and mucosal layers of the gut wall throughout the alimentary tract in each of the animal species examined. In the thoracic portion of the œsophagus, the external plexus was adventitial rather than subserous in position.

One of the most conspicuous features of the enteric plexus in the animals examined was the presence of medullated nerve fibres with axis cylinders which were relatively large in diameter (2–4 μ). The large fibres reached the gut wall in mesenteric fasciculi in company with finely medullated and unmedullated fibres which were either medium-sized (1–2 μ) or small (less than 1 μ) in diameter.

The large nerve fibres were more numerous in the œsophagus and terminal third of the large intestine than in the stomach, small intestine and proximal two-thirds of the large intestine. Excepting in the terminal portion of the large intestine, the large fibres terminated by branching

into medium-sized fibres in either the subserous or myenteric plexus. Consequently, most of the large fibres in the stomach and intestines were found in the subserous plexus near the attachment of the mesenteries. In the terminal portion of the large intestine, the intramural course of the large fibres was longer than in other parts of the gut and comparatively large fibres which branched into medium-sized fibres were found also in the submucous plexus.

The number of neurons in the myenteric plexus in each of the major subdivisions of the gut was greatly in excess of that in the submucous plexus. In rodents and rabbits, most of the enteric neurons were lightly stained in specimens impregnated with the silver technique used in this study (Plate LXXVII, fig. 1). In cats and primates, both darkly stained and lightly stained neurons were distinguished (fig. 2). In the myenteric plexus these varieties were approximately equal in number in the intestines, but the darkly stained cells were less numerous in the stomach. The cell bodies of the darkly stained neurons were larger than the lightly stained variety and most were multipolar in form, although many bipolar or unipolar cells were also seen. In the submucous plexus of the stomach and intestines, the darkly stained neurons were less numerous throughout than the lightly stained neurons; the former were usually either unipolar or bipolar (figs. 2, 3), while the latter were often multipolar in form (fig. 4).

Nerve fibres arising from enteric neurons were either medium-sized or small in diameter. Most of the fibres were either regular or slightly undulate in outline but some showed an occasional varicosity. In cats, the processes of darkly stained neurons were medium-sized in diameter near their origin whereas the processes of lightly stained neurons were of small diameter.

Specimens of gut were teased so that portions of the submucous layer could be examined with the basal portion of the mucous membrane (fig. 1). In rodents and rabbits, the submucous plexus was arranged in a tiered formation with fasciculi linking ganglia throughout the thickness of the comparatively thin submucous layer. In cats and primates, most of the submucous ganglia were adjacent to the circular muscle coat in the outer part of the comparatively thick submucous layer. Many of the fasciculi in both groups of animals contained nerve fibres which traversed the submucous plexus obliquely and branched as they passed towards the mucous membrane.

In thick frozen sections of the gut wall, many fasciculi were seen which linked the nerve plexuses of the various layers. Each fasciculus received fibres from neurons in either the myenteric or submucous plexus. It was sometimes possible to trace individual medium-sized nerve fibres which traversed the gut wall obliquely from the subserous layer through the intervening layers to the mucous membrane. However, most of the nerve

fibres which reached the submucous plexus from the subserous and myenteric plexuses travelled in fasciculi which accompanied blood vessels (fig. 6); the fibres then usually pursued an independent course through the submucous plexus, but some continued with the blood vessels into the mucous membrane. The fasciculi which accompanied blood vessels contained mainly medium-sized and small nerve fibres and the pattern of their branching was similar to that of the vessels they accompanied. Fasciculi which accompanied smaller blood vessels usually contained fewer nerve fibres, most of which were extremely fine (fig. 7). Many of the paravascular fasciculi were also joined by processes from neurons in either myenteric or submucous ganglia.

Many of the medium-sized nerve fibres in the submucous plexus terminated in the mucous membrane. The fibres branched repeatedly in the submucous plexus and again shortly after piercing the muscularis mucosæ, often in company with small nerve fibres. Some of the fibres formed coils of varying complexity in the submucous layer and others followed a course parallel to the muscularis mucosæ for considerable distances before branching. The mucosal branches of the fibres were often traced for considerable distances in the subglandular and interglandular connective tissue, but it was never possible to follow them to their terminations for they became so fine that they were lost to view against a background of epithelial or smooth muscle cells which themselves showed some degree of argyrophilia (fig. 8). Indeed, it was not possible to demonstrate the termination of nerve fibres in any part of the gut. They remained discrete as far as they could be traced and there was no evidence that they entered an anastomotic or reticular network. Enteric neurons were not seen in the mucous membrane and Schwann cell nuclei accompanying nerve fibres were seen only rarely.

The neurons in the submucous ganglia were frequently arranged in the form of a capsule about a core of mainly small nerve fibres which were continuous with fasciculi which entered the mucous membrane. In rats, processes from neurons in ganglia situated immediately subjacent to the muscularis mucosæ were traced through this layer into the mucous membrane (fig. 5). In specimens from cats, processes from large unipolar or bipolar neurons often branched shortly after leaving the ganglia; some of the branches were traced as far as the muscularis mucosæ while others entered fasciculi which linked the submucous and myenteric plexuses (figs. 2, 3).

Many fibres in the enteric plexus were irregular in outline; large fibres were usually undulate throughout their length, while some of the medium-sized fibres were slightly varicose at irregular intervals. In cats, the varicosities were often lightly stained at their centres and occurred more frequently on the fibres during their course through enteric ganglia. Filamentous processes from lightly stained neurons sometimes appeared

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to terminate at the varicosities on the fibres as they traversed submucous ganglia (fig. 3).

The appearances of the submucous and mucous plexuses in some parts of the gut were different from the appearances in other parts. Thus, in the *œsophagus*, enteric ganglia were not present in the submucous plexus, which consisted mainly of bundles of medium-sized nerve fibres, some of which were continuous with fasciculi in the adventitial coat. Nerve fibres left the parent bundles at varying depths in the submucous layer and passed independently towards the mucous membrane where their fine terminal branches entered the basal layer of the epithelium (fig. 9). Small nerve fibres which ramified in the open-meshed muscularis mucosæ and about fine blood vessels were also seen.

In the nonglandular part of the *stomach* of the rodents, the submucous and mucous plexuses were similar in appearance to those in the œsophagus. In the glandular portion of the stomach of the rodents and in the stomach of the other animals examined, the larger submucosal fasciculi frequently were unduloid in outline (fig. 10), while the smaller fasciculi were often arranged in loops. Both types of bundles were joined by processes from neurons in the submucous ganglia. Individual medium-sized nerve fibres were also seen, which formed coils of varying complexity in the submucosa before piercing the muscularis mucosæ to enter the mucous membrane. Many small nerve fibres in the mucous membrane were seen lying apparently in contact with the basal aspect of the epithelial cells including argentophil cells (fig. 11). The terminations of these fibres were not seen for they became progressively smaller in diameter until they were lost to view.

In the *small intestine*, medium-sized nerve fibres terminating in the mucous membrane were less numerous than in the stomach and coiled fibres were seen only infrequently. In the proximal two thirds of the *large intestine*, the arrangement of the submucous and mucosal plexuses was similar to that in the small intestine, excepting that medium-sized fibres which formed coils were more numerous (fig. 12). In the terminal third of the large intestine, there were appreciably fewer neurons in the submucous plexuses than elsewhere in the intestines, and large nerve fibres were also seen in the submucous layer. Some of the mucosal branches of the large fibres were traced as far as the surface epithelium, between the openings of the intestinal glands (fig. 13), and other branches ramified on the basal aspect of cells of the glandular epithelium (fig. 14).

Darkly stained spherical or spindle-shaped structures were seen occasionally in fasciculi and ganglia of the enteric plexus (fig. 15). They are of interest because of their resemblance to remnants of nerve fibres which were seen much more frequently after denervation experiments on the gut.

Experimental Observations

(1) *Changes in the Small Intestine after Division of Mesenteric Neurovascular Bundles*

In rats.—There was an appreciable reduction in the number of nerve fibres at the middle of the operated segment of small intestine within twenty-four hours and a more pronounced reduction within three days after division of mesenteric nerves. This reduction involved the plexuses in each layer of the intestine but was more conspicuous in fasciculi which accompanied blood vessels. The enteric plexus at the proximal and distal extremities of the operated segment was indistinguishable from that in unoperated portions of the small intestine.

Within eight hours after operation, many of the nerve fasciculi in the operated segment contained fibres which were swollen intermittently along their length. In many neurons, the cytoplasm was more darkly stained than that of neurons in unoperated portions of the gut.

Within twenty-four hours, there were obviously fewer medium-sized nerve fibres in the operated segment than in normal portions of the small intestine. Some of the fibres consisted of spindle-shaped swellings and varicosities linked by thread-like strands of axoplasm which could often only just be resolved by the light microscope. The swellings were frequently large and irregular at points where the fibres bifurcated. Remnants of nerve fibres which consisted of relatively large, darkly stained swellings continuous with attenuated nerve fibres were also seen (fig. 16). The attenuated fibres were often regular in outline but became progressively thinner until at varying distances from the swellings they were no longer visible. The degenerated fibres appear to have undergone a process of axoplasmic retraction, rather than fragmentation, at intervals along their length.

The appearances of the enteric plexus at thirty-six hours, at forty-eight hours, and at seventy-two hours after operation were similar to those seen after twenty-four hours, except that there was a progressively greater reduction in the number of nerve fibres in the operated segment (fig. 17). This reduction was not accompanied by a corresponding increase in the number of fragmented fibres, most of which had disappeared apparently without leaving any trace in the now depleted fasciculi. However, there were many darkly stained fibre remnants which were spherical or spindle-shaped and some of these resembled the structures which were seen very much less frequently in normal animals (fig. 15). No further reduction in the number of nerve fibres was seen in rats which survived longer than three days after operation, although some few fibre remnants persisted for as long as six days.

Nerve fibres which were normal in appearance were seen in the mucous membrane at the centre of the operated segment in all the rats examined and some were traced to an origin from neurons in submucous ganglia.

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An examination of the gut was made in rats in which four or five consecutive neurovascular bundles had been ligated and divided. Following this procedure, there was a dramatic change in the microscopic appearance of the gut within eight hours after operation. Many of the small veins at the middle of the operated segment were engorged with blood cells, and tissue cells showed an altered form and staining reaction suggestive of degenerative changes. Most of the nerve fibres at the middle of the operated segment were fragmented and consisted of darkly stained particles arranged in rows (fig. 18). There was a progressive disappearance of these fragmented nerve fibres between twenty-four and forty-eight hours after operation, and, after two days, fibre-tracts were seen which consisted of pale nucleated bands containing comparatively few intact nerve fibres most of which were traced to an origin from lightly stained enteric neurons. In one animal which survived five days after operation, shedding of the superficial layers of the mucous membrane at the middle of the operated segment had occurred followed by regeneration of glandular epithelium. Nerve fibres from adjacent portions of the operated segment of small intestine were followed as far as the mucous membrane of the ulcerated region where some of the fibres partially encircled intestinal glands (fig. 19). Branches of some of these fibres terminated in growth cones subjacent to the regenerating epithelium while other branches insinuated between regenerating epithelial cells arranged in layers and became progressively so fine that they were lost to view (fig. 20).

In cats.—The effect of interruption of mesenteric fasciculi on the appearance of the enteric plexus at the middle of the operated segment was less conspicuous in the cat than in the rat, except in fasciculi accompanying blood vessels. Within five days after operation, there was a striking reduction in the number of large and medium-sized nerve fibres in association with larger blood vessels and in the number of medium-sized and small nerve fibres in fasciculi accompanying smaller blood vessels. There was also an appreciable but less striking reduction in the number of medium-sized nerve fibres in the principal fasciculi of the myenteric plexus and in the submucous and mucous plexuses.

Fragmented large nerve fibres were seen after an interval of three days in fasciculi accompanying large blood vessels in the serous layer near the attachment of the mesentery. Fasciculi in this situation contained remnants of large fibres for as long as five days after operation (fig. 22). Fragmented large fibres from some of the paravascular fasciculi joined fasciculi in the myenteric plexus where they were traced through several generations of branches. With successive branching, the fragments of the fibres became progressively smaller in size and ultimately were lost to view between the fibres of the myenteric plexus, the great majority of which were normal in appearance.

Degenerative changes in small and medium-sized nerve fibres also were seen in fasciculi accompanying blood vessels in the operated segment of gut. Fragmented or beaded fibres occurred within thirty-six hours, and spherical fibre-remnants, some of which were arranged in series, occurred within two days after operation (figs. 23–25). Spindle-shaped fibre-remnants, which resembled the axoplasmic retraction forms found in rats, were seen frequently in both the submucous and mucous layers of the operated segment and persisted for as long as seven days after operation.

Processes from some of the large multipolar neurons in the myenteric plexus were markedly irregular in outline, due to the presence of lateral axoplasmic protrusions, from three to seven days after operation (fig. 21), and processes from many other neurons were markedly beaded from three to fourteen days after operation. However, the neurons of the submucous ganglia were not appreciably different in form from those in unoperated segments of the small intestine.

A careful examination was made of the enteric plexus in portions of small intestine both proximal and distal to the middle of the operated segment. No degenerating nerve fibres were seen beyond the limits of the operated segment.

There were many medium-sized and small nerve fibres in submucous and mucous layers at the middle of the operated segment which were normal in appearance up to fourteen days after division of four mesenteric neurovascular bundles. In frozen sections of the gut, medium-sized nerve fibres from neurons in submucous ganglia were traced as far as the muscularis mucosæ, where they were apparently cut in the plane of the section; other fibres which were not connected to neurons in the section, pierced the muscularis mucosæ and entered the mucous membrane; still other fibres were seen only in the mucous membrane. Many small nerve fibres from paravascular fasciculi reached adjacent blood vessels where they ramified between smooth muscle fibres (fig. 26); others were seen in the subglandular and interglandular connective tissue of the mucous membrane.

(2) *Examination of Nerve Fasciculi in the Mesentery of the Small Intestine*

Specimens were taken from rats and cats in which individual mesenteric neurovascular bundles had been divided between ligatures. Portions of the bundles both central and peripheral to the incision, as well as portions of normal bundles taken at a distance of at least 10 cm. from the mesenteric incision, were stained in block and sectioned longitudinally at 8 μ after embedding in wax.

In unoperated portions of the mesentery.—There were usually at least 2 large nerve fasciculi and several smaller anastomosing fasciculi within each neurovascular bundle. Some of the bundles contained ganglia

which were situated within or adjacent to the nerve fasciculi. Each ganglion contained from two to twelve small lightly stained neurons which were multipolar in form. In rats, almost all of the mesenteric nerve fibres were finely medullated or unmedullated and were either medium-sized (1–2 μ) or small (less than 1 μ) in diameter. In cats, in addition to medium-sized and small fibres, there were a number of thickly medullated nerve fibres in which the axis cylinders were comparatively large in diameter (2–4 μ, fig. 27).

In operated portions of the mesentery.—(i) Peripheral to the mesenteric incision: In rats, most of the nerve fibres disappeared within three days. In spite of the striking reduction in the number of fibres, comparatively few degenerated fibres were seen at any one time after operation. In cats, many medium-sized and small nerve fibres disappeared within three days after operation also but fibre-remnants were seen rather more frequently (fig. 28). All the large nerve fibres in cats were fragmented at three days and some of their remnants—now smaller in size—were still found at five days after operation (fig. 29). In the fasciculi of both groups of animals, there were medium-sized and small nerve fibres which were normal in appearance for as long as fourteen days after operation.

(ii) Central to the mesenteric incision: In cats, the largest nerve fibres were markedly irregular in outline within twenty-four hours after operation for their axis cylinders presented lateral protrusions which were arranged in series along the length of the fibres (fig. 30). The fibres were thus similar in appearance to processes of some of the neurons in the operated segment of small intestine. Nerve fibres with this appearance persisted for as long as fourteen days after operation. In tangential sections of the fasciculi some of the protrusions appeared to be divorced from the axis cylinders and resembled remnants of degenerated nerve fibres (fig. 31). However, each of the protrusions was completely surrounded by a portion of the myelin sheath and differed in this respect from the remnants of large nerve fibres which were seen in fasciculi peripheral to the mesenteric incision. Medium-sized and small nerve fibres in both cats and rats were not appreciably different in form from those in unoperated portions of the mesentery.

There was no convincing evidence of nerve degeneration and no apparent reduction in the number of nerve fibres in fasciculi proximal to the mesenteric incision in either cats or rats.

(3) *Changes in the Submucous and Mucous Plexuses after Division of Spinal Nerves Peripheral to Their Ganglia*

In rats.—After division of spinal nerves T6 to L4, nerve fibres in the submucous plexus of the œsophagus were normal in appearance in animals killed at intervals of up to four days after operation. Degenerated nerve fibres were seen within twenty-four hours in the submucous plexus of

both the stomach and small intestine and, although less common, were similar in appearance to those found in the small intestine after division of mesenteric fasciculi. Thus, nerve fibres consisting of varicosities linked by slender axoplasmic threads were seen, as well as spindle-shaped and spherical or piriform fibre-remnants which sometimes were quite large (fig. 32). A number of the neurons in the submucous ganglia of the stomach and small intestine showed an alteration in form and staining reaction similar to that found in the small intestine after division of mesenteric fasciculi. Small spherical or spindle-shaped remnants of nerve fibres were seen frequently in the mucous membrane of the stomach and much less frequently in the mucous membrane of the small intestine. After an interval of three days the appearance of the submucous and mucous plexuses in the stomach and small intestine of operated animals was not appreciably different from that in normal animals except for the presence of fibre-remnants, most of which were in paravascular fasciculi.

After division of all spinal nerves below L6, peripheral to their ganglia, there was a striking change in the appearance of the submucous and mucous plexuses in the terminal 3 cm. of the large intestine. The mucosal branches of large fibres were beaded within twelve hours after operation; most of the parent fibres in the submucous plexus were markedly irregular in outline after eighteen hours (fig. 33) and were fragmented at twenty-four hours after operation (fig. 34). Spindle-shaped and spherical remnants of nerve fibres were also seen in the submucous and mucous layers within twenty-four hours. Within three days after operation, almost all of the large nerve fibres of the submucous plexus had disappeared. However, there were some large fibres in the submucous layer and many medium-sized and small nerve fibres in both the submucous and mucous layers, which were normal in appearance at this time. Many of the medium-sized fibres which formed coils in the submucosa were also normal in appearance. Degenerated fibres were less frequent at more proximal levels in the large intestine, and the enteric plexus at a distance of 10 cm. from the anal margin appeared normal.

In cats.—After division of spinal nerves T5 to T11, peripheral to their ganglia, nerve fibres in the œsophagus and in the submucous and mucous plexuses of those portions of stomach which were examined were apparently unaffected by the operation. Large nerve fibres in both the mesentery and the subserous and myenteric plexuses of the portions of jejunum which were examined were fragmented after three days and resembled those illustrated in fig. 22. Degenerative changes involving only small fibres were also seen in the submucous and mucous layers of the jejunum within forty-eight hours (fig. 35), but the great majority of the nerve fibres in both submucous and mucous layers were normal in appearance up to four days after operation.

After division of all spinal nerves below L6, striking degenerative

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changes occurred in the submucous and mucous layers of the terminal portion of the large intestine, for a number of the large fibres in the submucous layer were fragmented at three days after operation. Fragments of nerve fibres, similar in appearance to those illustrated in fig. 34, were also seen in the mucous membrane. These remnants were thus larger in size than those seen in the mucous membrane of the small intestine after division of spinal nerves at a more rostral level. Fragmented large nerve fibres became progressively less frequent in the large intestine over a distance of 15 cm. from the anal margin. A number of large fibres were also seen which were apparently undergoing degenerative changes although they were not yet fragmented. However, there were many large fibres and also many small and medium-sized fibres (including some which formed coils) which were normal in appearance in the submucous and mucous layers of the terminal portion of the large intestine.

Discussion

In the present study, three categories of nerve fibres were recognized both in the enteric plexus throughout the gut and in the nerve fasciculi reaching the small intestine with mesenteric blood vessels. Most of the nerve fibres in the enteric plexus—certainly all of the processes of enteric neurons—were medium-sized (1–2 μ) or small (less than 1 μ) in diameter. Medullated nerve fibres, in which the axis cylinders were comparatively large in diameter (2–4 μ), reached the gut wall in mesenteric fasciculi in company with medium-sized and small nerve fibres, and terminated there by branching into medium-sized fibres in the subserous or myenteric plexus. In the terminal portion of the colon large fibres were also present in the submucous plexus. Thus, all the large nerve fibres but only a proportion of the medium-sized and small nerve fibres in the enteric plexus were extrinsic in origin.

It was not possible to demonstrate terminations in any of the enteric nerve fibres in the present study, even although individual nerve fibres in many situations were traced until they were no longer visible under the light microscope. Nerve filaments apparently can be traced to visible terminations if they are either heavily coated with metallic silver or swollen as a result of poisoning with methylene blue. These procedures have been used by a number of workers, but the artefacts so produced give an erroneous impression of the size (and possibly conformation) of enteric nerve fibres at their terminations. Indeed, Richardson has shown that the usefulness of silver impregnation and methylene blue techniques for demonstrating enteric nerve fibres is limited, for many of the fibres are manifestly too small in diameter to be resolved satisfactorily by the light microscope.

No evidence of a syncytial arrangement of fine nerve fibres was found in any part of the gut. A comparison of photomicrographs of the arrange-

ments of nerve fibres in the present study, with various forms of neural syncytia, as for example, figured by Jabonero and Meyling, suggests that the so-called syncytia are artefacts. The structures described by Jabonero (1958, fig. 19) in silver-impregnated material appear to be bundles of fine fibres (surrounded by impregnated Schwann elements) which are stained at intervals along their length, and the specimens of gut stained with methylene blue in which Meyling describes a syncytium of "interstitial" cells cannot be considered free from artefacts when judged by the criteria of Weddell and Zander (1950) and Weisse (1958) using phase-contrast microscopy.

Most of the investigators who have described changes in enteric nerve fibres following degeneration experiments appear to have been concerned mainly with large nerve fibres which show Wallerian degeneration characteristic of "medullated" nerve fibres. In the present study, degenerative changes in medullated nerve fibres, similar to those described by previous investigators, occurred in the enteric plexus within three days after division of either mesenteric fasciculi or spinal nerves. However, many medium-sized and small nerve fibres which appeared unmedullated under the light microscope were also severed when mesenteric neurovascular bundles were divided and these showed degenerative changes which were not only frequently different in form from the degenerative changes in large nerve fibres, but also earlier in the times of their onset and completion. Thus, many medium-sized and fine fibres in operated segments of gut appear to undergo a process of axoplasmic retraction, rather than fragmentation, resulting in the formation of spindle-shaped swellings connected by slender threads of axoplasm. The connecting threads eventually disappear and the course of the degenerated fibres is then represented by spherical darkly stained remnants arranged in series. In other degenerating fibres there appeared to be a flow of axoplasm to points at which they branch, so that remnants of the fibres consisted of comparatively large swellings which were darkly stained. The phenomenon of axoplasmic retraction in degenerating axis cylinders is possibly dependent on the viability of surrounding tissue elements, for unmedullated nerve fibres which had degenerated in specimens of the gut in rats, in which the blood supply was impaired, were all fragmented. If it can be assumed that no dilution of axoplasm occurs during the process of retraction in unmedullated enteric fibres, the amount of axoplasm in a spherical remnant which is 10 μ in diameter would be equivalent to that in a nerve fibre which is 2 μ in diameter and over 150 μ in length. Such a process would account for the fact that comparatively few fragmented nerve fibres were seen in many regions of the gut during a period of from one to three days after operation, even although there was a progressive reduction in the number of medium-sized and small fibres during this period. The present observation that degeneration in unmedullated

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nerve fibres begins within twenty-four hours after operation is thus in agreement with the findings of Langley and Anderson and Tuckett, but it is clear that the process is not completed, in some of the fibres, until three days after operation.

Both medium-sized and small nerve fibres occur in the submucous and mucous plexuses, but the medium-sized fibres were the principal subject of study because they could be traced for greater distances. Many medium-sized fibres in the submucous plexus are processes of neurons in the submucous ganglia; others originate in myenteric neurons or reach the gut in mesenteric fasciculi. In rats, many neurons are situated immediately subjacent to the muscularis mucosæ and it was possible at times to trace their processes through the muscularis mucosæ into the mucous membrane. In cats, there was no direct evidence of continuity between submucous neurons and medium-sized fibres in the mucous membrane; this may have been due to the difficulty in tracing the processes of the neurons throughout their course, for most of the neurons are situated in ganglia in the outermost part of the submucous layer. Many nerve fibres which were normal in appearance persisted in the submucous and mucous layers at the centre of the operated segment of small intestine for as long as fourteen days after division of four mesenteric neurovascular bundles. Fibres from neurons in submucous ganglia in the operated segment were traced as far as the muscularis mucosæ where they were cut in the plane of the section; other fibres not connected to neurons pierced the muscularis mucosæ and entered the mucous membrane; and still other fibres were seen in the mucous membrane only. Downman has shown in physiological experiments on cats that the length of small intestine innervated by constituents of mesenteric nerve bundles is indicated approximately by the distance between the centres of adjacent arterial arcades and that the territories of adjacent mesenteric nerve bundles overlap by up to 20 per cent of the length of each territory. Downman's observations have been confirmed histologically in the present study for degenerated nerve fibres were not found beyond the limits of the operated segment of intestine after division of mesenteric neurovascular bundles. It is thus unlikely that any of the nerve fibres which persist in the mucous membrane at the middle of the operated segment, after division of as many as four neurovascular bundles, are extrinsic in origin. It is possible that neurons in myenteric ganglia also innervate the mucous membrane for processes from many of the cells in both rats and cats can be traced as far as the submucous plexus.

In specimens from the small intestine in a rat in which shedding of a portion of the mucous membrane had occurred after cutting five mesenteric neurovascular bundles, it is interesting to note that there was an invasion of nerve fibres from adjacent portions of the operated segment of gut, and that the invading fibres terminated in branches which insinuated

themselves between cells of the regenerating glandular epithelium. Although they were not traced back to their origins it is possible that these fibres are processes from enteric neurons, for the ulcerated portion was situated at the middle of the operated segment. It is obviously impossible to determine the functional significance of neurons which innervate the mucous membrane solely by morphological study. However, there is physiological evidence which suggests that nerve impulses transduced at the mucous membrane of the small intestine are conveyed to intestinal musculature through intra-mural nerve pathways which include at least one synaptic interruption (Bülbring, Lin and Schofield). This evidence, when taken in conjunction with the findings in the present study, strongly suggests that the mucosal processes of at least some of the enteric neurons of the small intestine give rise to fibres which terminate in relation to epithelial cells in the mucous membrane, and also that enteric neurons which innervate the mucous membrane in this way are afferent in nature. This, however, does not mean that mucosal processes of other enteric neurons do not terminate in relation to intramucosal extensions of the muscularis mucosæ or even blood vessels; on the contrary, many nerve fibres were seen to ramify on blood vessels in the submucous and mucous layers of the operated segment of small intestine.

Kuntz and Jacobs (1955) have shown that neurons aggregated in ganglia occur in the mesentery of the colon, and the present study shows the same to be true of the mesentery of the small intestine. However, too few neurons were present in the distal portions of severed mesenteric fasciculi to account for the number of apparently normal medium-sized and small nerve fibres which persisted in this situation. Furthermore, all of the neurons in the mesenteric ganglia were small in size and all of their processes were small in diameter. It is a reasonable assumption therefore, that all of the medium-sized fibres and most of the small fibres which were found in the distal portions of severed mesenteric fasciculi were centripetal processes of enteric neurons. In this respect the present findings are in agreement with those made by Graham Ross. However, until further studies have been made, it is not possible to say whether the fibres which pass centripetally from the gut are central processes of neurons which also give rise to mucosal processes.

Denny-Brown and Brenner (1944) and Weiss and Hiscoe (1948) have shown that when a nerve trunk is constricted, changes occur in nerve fibres proximal to the level of constriction so that their axis cylinders become markedly irregular in outline due to the development of lateral protrusions. According to Weiss and Hiscoe and Van Breeman, Anderson and Reger (1958), these changes are due to an interruption in the centrifugal flow of axoplasm in the fibres. In cats, large nerve fibres which were similar in form to those described by the above authors appeared within twenty-four hours in mesenteric fasciculi proximal to the point at which

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they were ligated. Comparable changes—although later in onset and only temporarily present—also occurred in medium-sized fibres arising from enteric neurons in the operated segment of small intestine (i.e. distal to the point of ligation). It is of interest that the enteric fibres with lateral protrusions resemble processes of Purkinje cells in which gemmules are described as normal features. If the alteration which was seen in the form of the extrinsic and intrinsic fibres is due to the same process, then ligation of mesenteric fasciculi resulted in construction not only in large mesenteric fibres in which the axoplasmic flow is centrifugal but also in medium-sized fibres, arising from enteric neurons, in which the axoplasmic flow is centripetal. Differences in both the times of onset and duration of the changes in the mesenteric fibres, on the one hand, and the enteric nerve fibres, on the other, might well be due to differences in either the metabolic activity of the respective parent neurons or the number of alternative channels available for the dispersal of their cytoplasmic substances. However, the possibility cannot be excluded at present that the alteration in the form of the enteric neurons which was seen after ligation of mesenteric fasciculi was due to other influences, such as, for example, interruption of their preganglionic nerve supply.

It is clear that some of the nerve fibres which originate either in spinal ganglia or in the spinal cord, must terminate in the mucous membrane of the stomach and intestines. Thus, in the terminal portion of the large intestine, degenerative changes are evident both in large submucosal fibres and in their mucosal branches after division of lower lumbar and sacral spinal nerves, peripheral to their ganglia. In the small intestine of the cat, on the other hand, although large nerve fibres reaching the gut in mesenteric fasciculi were fragmented after division of thoracic spinal nerves peripheral to their ganglia, the degenerative changes involved only small nerve fibres in the mucous membrane. This finding was not unexpected for, unlike the terminal portion of the large intestine, large fibres do not occur in the submucous layer of the small intestine; nevertheless, it explains, in part, why so little emphasis has been placed in previous neurohistological investigations on the gut on the presence of extrinsic nerve fibres in the mucous membrane of the small intestine. It is unlikely that the mucosal fibres which degenerated after division of spinal nerves were preganglionic in nature, for no nerve cells were found in the mucous membrane. Spoerri (1949), it is true, has described a variety of "interstitial cells of Cajal" in the gastric mucous membrane, which she believes are neurons. Although there is no certainty as to the nature of these cells, they are more commonly known as argentophil cells and are a well-known component of the gastro-intestinal epithelium (Schofield, 1953). It is likely therefore that fibres from spinal nerves which terminate in the mucous membrane are processes of neurons in spinal ganglia, rather than from the spinal cord, and that they are afferent in nature.

Further studies will be necessary to determine the source of the many fibres in the mucous membrane which—although extrinsic in origin—do not arise from the spinal cord or spinal ganglia at the levels at which spinal nerves were divided. In the small intestine there is an appreciably greater reduction in the number of nerve fibres in the submucous and mucous plexuses after division of mesenteric fasciculi, than there is after division of spinal nerves. Similarly, in the mucous membrane of the terminal portion of the colon there are many fibres which are not affected by division of spinal nerves. The observations of Paintal and Iggo suggest that some of the fibres in the mucous membrane of the stomach and intestines are vagal in origin and preliminary findings from animals in which the vagus nerves were divided indicate that this is indeed the case. However, if it can be shown in further experiments that enteric neurons project centripetally in the vagus nerve as well as in mesenteric fasciculi, it may be necessary to reassess conclusions derived from physiological studies on the distribution of extrinsic nerve fibres which "reach" the gut in these nerves.

Summary

(1) The enteric plexus in a number of mammals (*Mus*, *Rattus*, *Cavia*, *Oryctolagus*, *Felis*, *Macaca*, *Papio*), and nerve fasciculi in the mesentery of the small intestine of rats and cats, have been examined in specimens stained with a silver impregnation technique.

(2) Enteric and mesenteric nerve fibres are classified, according to the diameter of their axis cylinders, into large fibres (2–4 μ), medium-sized fibres (1–2 μ) and small fibres (less than 1 μ). Nerve fibres arising from enteric neurons are either medium-sized or small in diameter.

(3) Changes in the appearance of enteric and mesenteric nerve fibres are described in rats and cats in which either mesenteric neurovascular bundles, or spinal nerves peripheral to their ganglia, were divided at operation.

(4) Histological examinations of the gut of normal and experimental animals lead to the following conclusions:

(*a*) Large nerve fibres in the gut are extrinsic in origin; some of the fibres arise in spinal ganglia and terminate in the mucous membrane of the stomach and intestines.

(*b*) The mucous membrane is innervated also by enteric neurons some of which are in ganglia of the submucous plexus.

(*c*) There are many nerve fibres in the mucous membrane which, although extrinsic in origin, do not arise from either the spinal cord or spinal ganglia at the levels at which spinal nerves were divided in the present study.

(*d*) Nerve fasciculi in the mesentery of the small intestine contain a number of nerve fibres which are centripetal processes from enteric neurons.

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(5) Evidence that some of the enteric neurons innervate the epithelium of the mucous membrane of the small intestine is presented in support of previous findings by Bülbring, Lin and Schofield which suggest that some enteric neurons are afferent in nature and mediate in the peristaltic reflex.

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LEGENDS FOR PLATES

PLATE LXXVII

FIG. 1.—Part of the submucous plexus from the duodenum of a normal rat. Medium-sized nerve fibres can be seen traversing a ganglion which contains lightly stained neurons.

FIG. 2.—A submucous ganglion from the jejunum of a cat. Darkly stained and lightly stained neurons are arranged in the form of a capsule about a core of nerve fibres. One of the darkly stained neurons is unipolar in form.

FIG. 3.—A neuron from the jejunum of a cat. The longer of the two processes of the cell was traced as far as the muscularis mucosæ.

FIG. 4.—From the jejunum of a cat. A lightly stained neuron which is multipolar in form can be seen in a submucous ganglion. Some of the fine processes of the neuron appear to terminate at lightly stained varicosities (marked with arrows) on a medium-sized fibre which is traversing the ganglion.

FIG. 5.—From the jejunum of a rat. A process from a neuron in the submucous layer has entered the mucous membrane after passing through the muscularis mucosæ (marked with an arrow).

FIG. 6.—From the jejunum of a rat. Nerve fasciculi traversing the submucous layer in company with blood vessels.

FIG. 7.—From the stomach of a guinea-pig. Medium-sized and small nerve fibres in a paravascular nerve fasciculus. Extremely fine nerve fibres (marked with arrow) can be seen passing to a blood vessel at the upper margin of the figure.

FIG. 8.—A medium-sized nerve fibre lying between intestinal glands in the mucous membrane of the jejunum of a cat.

FIG. 9.—From the œsophagus of a rabbit. Nerve fibres can be seen passing through the muscularis mucosæ to enter the epithelium at the lower margin of the illustration.

FIG. 10.—From the stomach of a rabbit. Nerve fasciculi in the submucous layer.

FIG. 11.—A nerve fibre in the mucous membrane in the glandular stomach of a rat. The fibre is apparently in contact with the base of an argentophil cell in the glandular epithelium.

FIG. 12.—A coiled fibre in the submucous layer of the large intestine in a rat.

FIG. 13.—From the terminal portion of the large intestine in a mouse. A nerve fibre can be seen lying subjacent to the surface epithelium of the mucous membrane.

FIG. 14.—From the same specimen as fig. 13. A nerve fibre ramifying on the basal aspect of epithelial cells of an intestinal gland.

FIG. 15.—A darkly stained swelling on an attenuated nerve fibre in the non-glandular stomach of a normal rat.

FIG. 16.—From the operated segment of small intestine in a rat, twenty-four hours after division of mesenteric neurovascular bundles. A darkly stained swelling, continuous with attenuated nerve fibres, can be seen in a fasciculus accompanying a blood vessel in the submucous layer.

FIG. 17.—Operated segment of small intestine in a rat, seventy-two hours after division of mesenteric neurovascular bundles. Myenteric plexus. A nerve fibre which consists of spindle-shaped swellings linked by slender threads of axoplasm, is illustrated. A darkly stained unipolar neuron can also be seen in a ganglion which contains only a few nerve fibres.

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PLATE LXXVIII

FIG. 18.—From the operated segment of small intestine in a rat, twenty-four hours after division of five mesenteric neurovascular bundles. Degenerated nerve fibres consisting of fragments arranged in rows can be seen in the myenteric plexus. Other tissue cells in the specimen also showed degenerative changes.

FIGS. 19 and 20.—From the middle of the operated segment of small intestine in a rat, five days after division of five mesenteric neurovascular bundles. Nerve fibres ramifying in the region of the regenerating glandular epithelium in the mucous membrane. In fig. 20, nerve fibres can be seen entering the epithelium.

FIG. 21.—From the operated segment of jejunum in a cat, three days after division of mesenteric neurovascular bundles. Lateral protrusions can be seen on nerve fibres which are processes of myenteric neurons (compare with fig. 30).

FIG. 22.—From the operated segment of jejunum in a cat, five days after division of mesenteric neurovascular bundles. A fragmented large fibre in one of the subserous fasciculi.

FIGS. 23 and 24.—From the operated segment of jejunum in a cat, twenty-four hours after division of mesenteric neurovascular bundles. Varicose nerve fibres in fasciculi of the submucous plexus.

FIG. 25.—Nerve fibre-remnants in small paravascular fasciculi in the submucous layer of the jejunum of a cat, two days after division of mesenteric neurovascular bundles.

FIG. 26.—Nerve fibres ramifying on a small submucoal blood vessel. Operated segment of jejunum of a cat, five days after division of mesenteric neurovascular bundles.

FIG. 27.—Large medullated nerve fibres in an unoperated nerve fasciculus in the mesentery of the small intestine of a cat.

FIG. 28.—Nerve fibre-remnants in the distal portion of a severed mesenteric fasciculus. Cat, three days after operation.

FIG. 29.—Remnants of a large nerve fibre in the distal portion of a severed mesenteric fasciculus. Cat, five days after operation. A number of intact nerve fibres and many nuclei can be seen in the depleted fasciculus.

FIG. 30.—A large nerve fibre, with lateral protrusions, in the proximal portion of a severed mesenteric fasciculus. Cat, thirty-six hours after operation.

FIG. 31.—From the same specimen as fig. 30. Tangential section of a fasciculus showing lateral protrusions which are separated from their parent fibres. The separated protrusions simulate degeneration in nerve fibres.

FIG. 32.—From the glandular stomach of a rat, twenty-four hours after division of spinal nerves. A darkly stained swelling at the level of the muscularis mucosæ.

FIG. 33.—Early degenerative changes in a large fibre in the submucous plexus of the terminal colon of a rat, eighteen hours after division of spinal nerves.

FIG. 34.—Remnants of a large nerve fibre in the submucous layer of the terminal colon of a rat, twenty-four hours after division of spinal nerves.

FIG. 35.—Remnants of nerve fibres in the mucous membrane of the jejunum of a cat, two days after division of spinal nerves.

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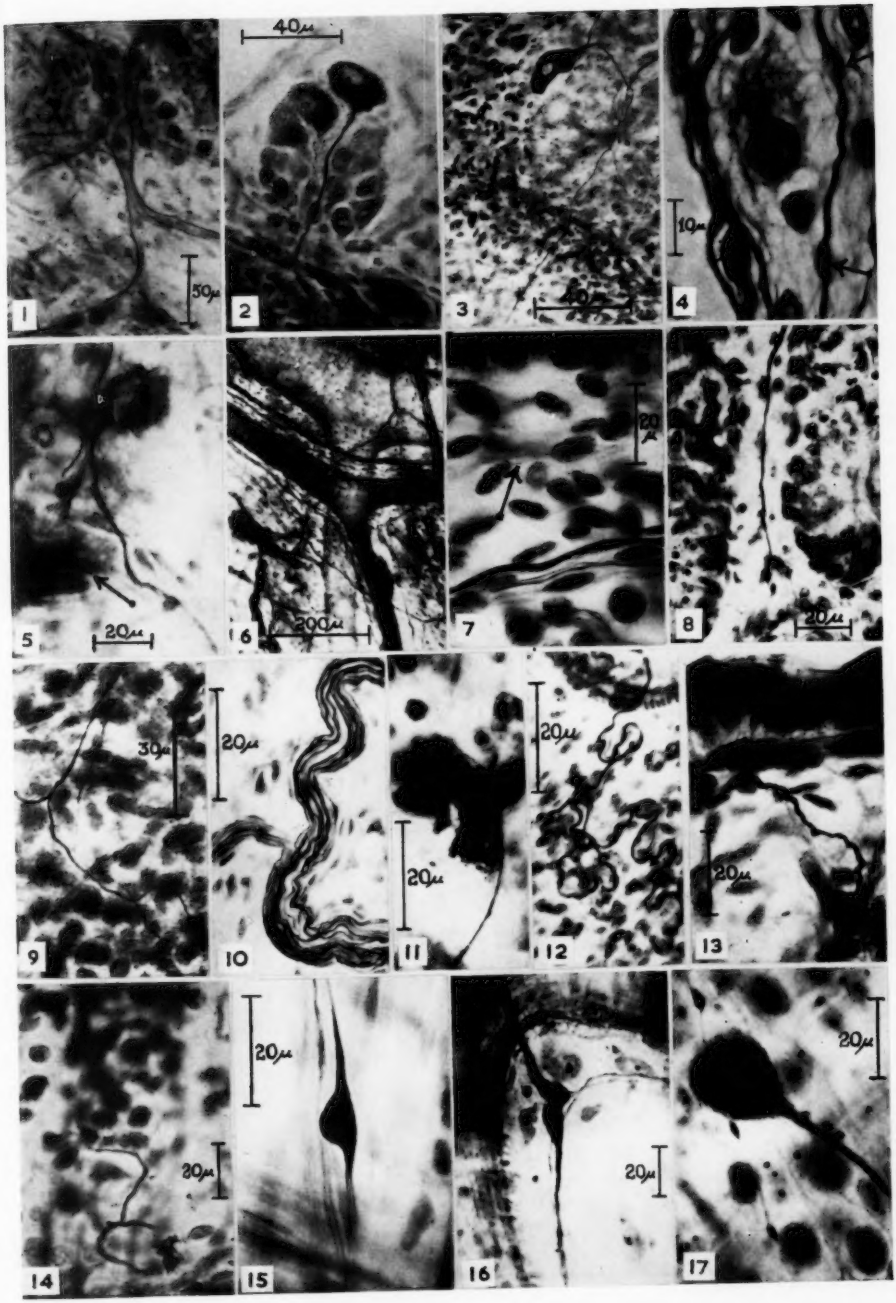
PLATE LXXVII



To illustrate article by G. C. Schofield.

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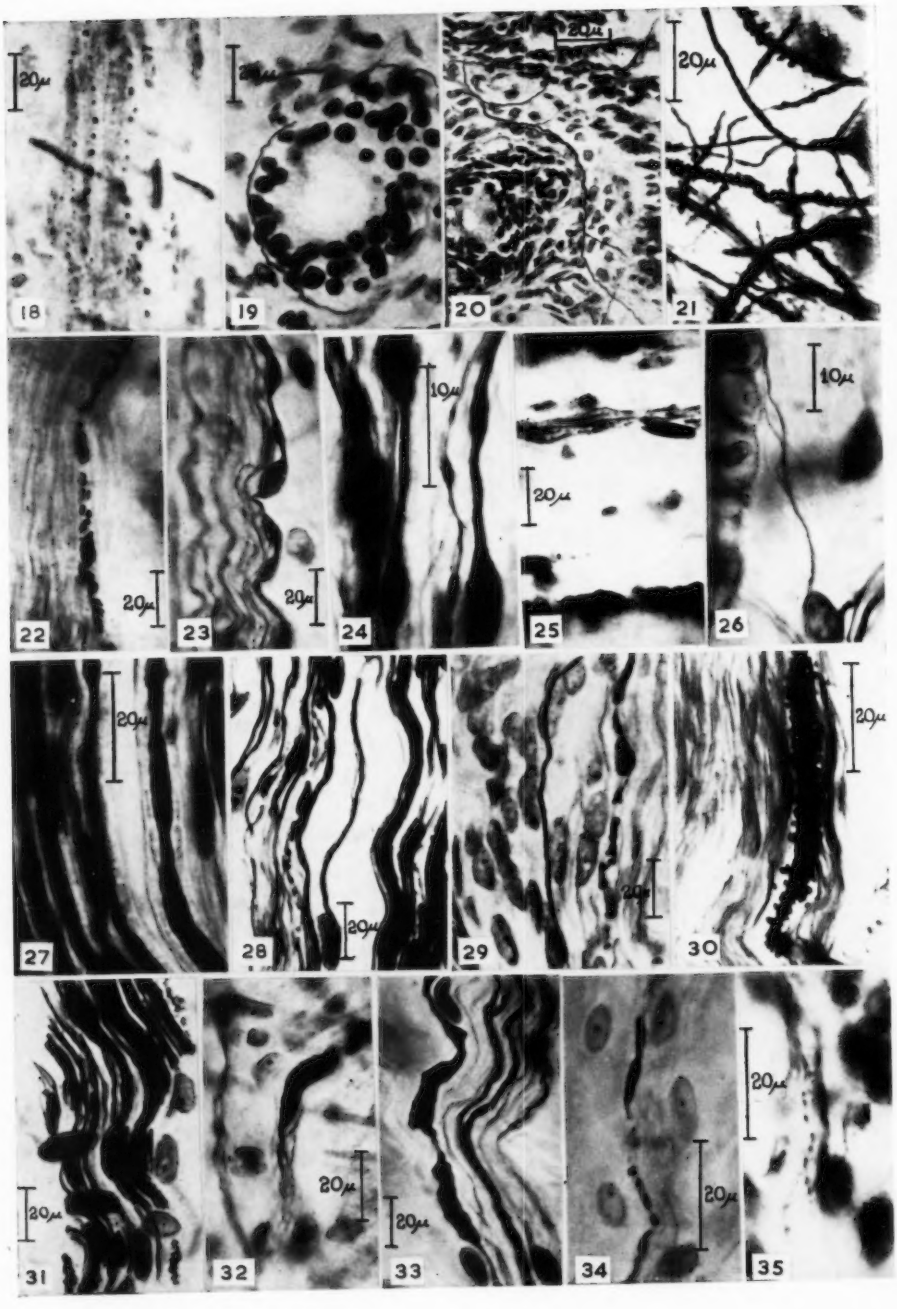

To illustrate article by G. C. Schofield.

NOTICES OF RECENT PUBLICATIONS

STEREOTAXIS

Introduction to Stereotaxis with an Atlas of the Human Brain. Edited by GEORGES SCHALTENBRAND and PERCIVAL BAILEY. 3 vols. Pp. 493, 230 illustrations, 76 plates with 34 attached and 14 removable overlays. Stuttgart: Georg Thieme Verlag. Price $233.35.

This work, written in English and German, was compiled by a distinguished American, German and Italian team. Its title can almost be said to conceal rather than reveal the grandeur and scope of its conception and accomplishment for, the atlas apart, it contains many detailed anatomical, physiological and pathophysiological descriptions of the cerebrum, brain-stem, hypothalamus, thalamus and basal ganglia, as well as sections given to electro-encephalography and the effects of electrical stimulation of deeper cell masses within the brain, stereotactic instruments and stereotactic surgery for extrapyramidal disturbances, among others.

Two of the three volumes are taken up by the atlas which was made from a number of brains selected from a total of 110 collected in Wurzburg and Lund. Many of the 34 macroscopical photographs are provided with fixed transparent overlays in two colours which are designed to show structural variations. In addition removable overlays, showing the maximum contours of the brain and ventricular system, are available and are easily superimposed on the relevant plates. The portion of the atlas given to the microscopical photographs commences with 23 frontal, horizontal and sagittal sections (4× magnification) through the basal ganglia, stained to show myelin sheaths. It is concluded in the 3rd volume which contains 19 large folded maps made from frontal and sagittal Nissl-stained sections magnified 20 times. All the plates and overlays are superlatively reproduced and the printing and production of the whole work is of the highest standard.

While the whole will surely be of the greatest value to neurosurgeons employing stereotactic techniques, the 1st volume in particular of this monumental work will interest many others, though for obvious reasons it is not likely to find its way on to many private bookshelves. In their introduction the editors refer to the years of intense effort devoted to its production; these years have not been wasted. It is a fabulous work.

J. H. PATERSON.

CONGENITAL MALFORMATIONS

Malformations Congénitales Du Cerveau. By G. HEUYER, M. FELD and J. GRUNER. 1959. Paris: Masson et Cie. Pp. 450.

No organ of the human body presents such a large number and wide variety of abnormalities of development as does the brain. We know that in most cases of severe mental retardation structural faults can be demonstrated. There has been a renewal of interest in this subject in recent years stimulated, no doubt, by the discovery of the effects of such factors as maternal rubella and irradiation. The more recent discovery that Mongolism depends on the presence of a single extra chromosome will serve to accelerate research in this field. Conferences in which representatives of diverse disciplines are brought together to present their viewpoints are being arranged.

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In July, 1959 there was the First International Medical Conference on Mental Retardation held at Portland, Maine, U.S.A. In July, 1960, we have the First International Conference on Congenital Malformations in London. In August, 1961, the Second International Conference on Mental Retardation will take place in Vienna.

The present monograph is based on papers given at an International Colloquium on Congenital Malformations of the Brain in Paris, in March, 1957. There are some thirty papers from French, German, Swiss, Dutch and Austrian workers.

A plea is made in the preface for more careful neurological studies of children with mental retardation, epilepsy and behaviour disorders. Their problems should be approached not so much from the position of adult psychiatry as from that of the neurologist, internist and pædiatrician.

In the first section there are papers on the normal development of the human brain, experimental embryology, and comparative neuropathology. There are examples of the ways in which arrested development of certain neural structures lead to particular malformations. The wide variety of agents which can induce embryopathy is stressed. There are two interesting examples of the Arnold-Chiari Malformation in a calf and a pig. In the former there was also an associated spina bifida and the author (Frauchiger, of Berne) points out that in the horizontally placed spinal cord of the calf, upward movement of the cord in relation to the growing vertebral column is minimal. The traction theory of production of the Arnold-Chiari Malformation, so often suggested in the human cases, can be rejected in the calf.

In the second section the question of ætiology is taken up and there are papers on infections of the fœtal brain, the role of rubella and of nutritional disorders. Further statistical studies are urged.

There is an authoritative summary of the morphological features of anencephaly, microcephaly, agenesis of the corpus callosum, hemiatrophy of the cerebellum and porencephaly by Minkowski of Zurich.

Of particular interest to clinicians is the chapter by Drs. Kissel, Dureux and Tridon on the neurological disturbances associated with malformations of the cranial and facial bones. It is well illustrated and documented. The association of anomalies of the eyes, ears, maxilla, mandible and digits with arrested development of the frontal lobes, the diencephalon and the base of the skull are a result of disturbances between the fifth and seventh week of embryonal life.

André-Thomas and de Ajuriaguerra of Paris contribute an excellent clinico-pathological description of eight cases of anencephaly with a survey of the recent literature. This detailed study (60 pp.) is in the tradition of classical French neurology.

There are shorter accounts of dysraphic lesions of the brain, malformations of the ventricles, hypoplasia and heterotopia of the cerebral cortex, hydranencephaly and hydrocephalus.

In his concluding remarks Dr. G. Heuyer draws attention to the necessity of studying the natural history of these cerebral malformations. Whether their origin is genetic, traumatic, infectious or toxic the subsequent evolution of symptoms and signs demands methodical investigation. He draws an analogy between the sequels of tuberculous meningitis in infancy—epilepsy, mental retardation, and behaviour disorders—and those of fœtal encephalitis. Delayed effects of supposedly static abnormalities such as aqueduct stenosis, basilar impression and agenesis of the corpus callosum also occur. A more dynamic approach is required.

Minkowski has said that every malformation of the brain is "a new creation." The value of an holistic approach to the whole subject is well exemplified by the papers in this monograph. It should provide much useful reading for the increasing numbers of clinicians, anatomists, embryologists, pathologists and geneticists interested in this branch of medicine.

J. D. SPILLANE.

STUTTERING

The Onset of Stuttering. By WENDELL JOHNSON and Associates. 1959. Minnesota University Press. London: Oxford University Press. Pp. 243. Price 40s.

Stuttering is a common and distressing condition about which little is known and the treatment of which is generally unrewarding. This report of research carried on at the University of Iowa from 1934–1957, is therefore to be welcomed. Much of the earlier work has already been reported but is summarized in this volume. The object of this research was to determine the age at which stuttering develops and the factors which contribute to its development. The parents of 250 stutterers and 250 non-stutterers were interviewed and compared on a basis of the interview and their scores on the Minnesota Multiphasic Personality Inventory. The results are reported in exhaustive detail: indeed tables constitute practically half of the book.

The conclusion of the book is that stuttering does not arise as is often supposed at any age between the onset of speaking and adult life as the result of injury, shock or fright, but that it arises at the age of 3–4 by "reference mainly to an interaction between a listener (usually the mother) and a speaker in which the listener made a distinctive perceptual judgmental reaction to the speaker's non-fluencies". "The parents are motivated to evaluate the non-fluencies as unacceptable or distressing, and to classify them as stuttering." It is said that once these interactions have been set in play, their effect is cumulative. Treatment is by breaking this vicious circle by parental counselling.

ELIOT SLATER.

SHORTER NOTICES

Critical Incidents in Psychotherapy. By STANLEY W. STANDAL, Ph.D. and RAYMOND J. CORSINI, Ph.D. 1959. New York: Prentice-Hall Inc. Price $6.95.

Psychotherapy is so subjective and intangible that by its very nature there is a lack of organized generally accepted knowledge that can be communicated to would-be psychotherapists. This book makes a novel approach to this problem. A number of psychotherapists took from their practice a case showing a "critical incident" and describe how they dealt with this situation. These reports were then submitted to 28 psychiatrists, psychotherapists and psychologists for comment and these were collated to form this book. It is interesting to note how the commentators succeed in fitting the critical incident and its proper handling into such varied theoretical frameworks as Freudian, Adlerian, Jungian, Rankian, Gestalt, Existentialist, Logotherapeutic, "client-centred", and so on. Each case is discussed by at least five of the experts and it is revealed how modern therapists think about these common problems—in their various ways. It is indeed a cross-section of present-day psychotherapy in America.

It also casts a light on current methods of handling patients in the United States. The third patient was diagnosed by the "school psychologist" as a paranoid schizophrenic on the basis of a Rorschach test and referred for psychotherapy to a counselling centre.

Massage, Manipulation and Traction. Ed. SIDNEY LICHT, M.D., ELIZABETH LICHT, Publisher, New Haven. Pp. 275. $10.0.

A representative group of fourteen exponents of physical medicine from England, Europe and America have presented a number of essays upon the application of physical methods of treatment, under the three broad headings in the title. There is for instance a chapter on the use of active and passive stretching by Squadron Leader Wynn Parry, on the benefits of percussion by Dr. Ritchie Russell, and one upon the

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clinical applications of massage by Dr. James Cyriax. All are by their nature stimulating, and show a therapeutic zeal which does not pervade all neurological centres.

Practical Neurological Diagnosis with Special Reference to the Problems of Neurosurgery. By R. GLEN SPURLING, M.D. 6th Ed. Pp. 284. Oxford: Blackwell Scientific Publications. Price 54s.

This simple little book fills its role of an introduction to neurological method. It is extremely elementary, but to reach 6 editions in twenty-five years it must satisfy a real need. It is concise, clear, and very well presented and illustrated.

Primary Tumours of the Calvaria, with Special Consideration of the Clinical Problems. By FRANKLIN JELSMA, M.D. 1960. Pp. 114. Oxford: Blackwell Scientific Publications. Price 56s.

The occurrence of benign and malignant tumours of all sorts, which erode the vault is analysed. Forty-four benign and five malignant tumours which were encountered in Louisville, Kentucky are described and related to the scanty literature. The little monograph is confined to a serial description of this specialized group of cases.

Selected Papers of Sir Geoffrey Jefferson. Pitman Medical Publishing Company, Limited. 1960. Pp. 563. Price 5 guineas.

Many will congratulate the publishers on their initiative in persuading Sir Geoffrey Jefferson to republish what is described as "all that is best" in his writings. The first section consists of philosophical reflections and the second of historical portraits. The third, and largest section, is naturally devoted to his scientific publications and includes his classical contributions to neurology and neurosurgery. Finally, there are two brief autobiographical sketches, one describing a return to Russia after more than forty years, and the other "on being happy and liking it." Sir Geoffrey says his life "has been the greatest fun." Here then the reader will find the wisdom and experience of a great clinician distilled from that unique spirit which is Geoffrey Jefferson.

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